STATISTICAL ANALYSIS PLAN

Open Label, Randomized, Controlled Phase 2 Proof-of-Concept Study of the Use of Favipiravir Compared to Standard of Care in Hospitalized Subjects with COVID-19

Protocol FAVI-COV-US201

Protocol Number:	FAVI-COV-US201
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Name of Test Drug:	Favipiravir
Phase:	Phase 2
Methodology:	Open-label, Randomized, Controlled, Proof-of-Concept
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Analysis Plan Date:	15 December 2020
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APPROVAL SIGNATURE PAGE

Protocol Title: Open Label, Randomized, Controlled Phase 2 Proof-of-Concept Study of the Use of Favipiravir Compared to Standard of Care in Hospitalized Subjects with COVID-19

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Approval Signature	Job Title

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory: FUJIFILM Pharmaceuticals U.S.A., Inc.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
BID	Twice daily
CI	Confidence interval
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECMO	Extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FCS	Fully conditional specification
FiO2	Fraction of inspired oxygen
ICH	International Council for Harmonisation
ICU	Intensive care unit
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
MAR	Missing at random
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NEWS2	National Early Warning Score 2
PaO2	Pressure of oxygen
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMM	Predicted mean Matching
PP	Per protocol
Rel Day	Relative study day
RM ANOVA	Repeated measures analysis of variance

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOC	Standard of care
SpO_2	Oxygen saturation
TCID50	Median Tissue Culture Infectious Dose at 50% cell infection
TEAE	Treatment-emergent adverse event
TTCR	Time to clinical recovery
ULN	Upper limit of normal
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Favipiravir is a small molecule, novel antiviral agent discovered by FUJIFILM Toyama Chemical Co., Ltd. It is a broad-spectrum antiviral that includes activity against all RNA virus families tested, including rabies, Ebola, Lassa, and coronaviruses. It has been in clinical trials for influenza, Severe Fever with Thrombocytopenia virus, Ebola, and has been used under compassionate release for Ebola, rabies, Lassa fever, norovirus, severe acute respiratory syndrome and the novel coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes the coronavirus disease of 2019 (COVID-19).

There is a global pandemic caused by SARS-CoV-2, threatening the lives of many and resulting in the need for well-tolerated molecular agents to speed cessation of viral shedding and ultimately recovery from COVID-19. SARS-CoV-2 causes disease ranging from mild, cold-like symptoms to acute respiratory failure and death. Epidemiologic studies are underway to determine whether individuals can be asymptomatic and transmit disease. There is currently no available approved treatment for COVID-19. People who have been hospitalized to treat acute respiratory symptoms in the US have no proven option other than supportive care, which includes mechanical ventilation, oxygen therapy, and treatment of coinfections and organ failure if needed.

Evidence from nonclinical (cell culture) experiments and recently reported clinical experience in China indicates that favipiravir may have clinical benefit in subjects infected with SARS-CoV-2. Prior influenza research indicated faster cessation of viral shedding and faster recovery for subjects treated with favipiravir than with placebo control. The safety profile of favipiravir is well-established. It is generally safe and well-tolerated except for transient elevations of uric acid that resolve with cessation of dosing. The risk-to-benefit assessment of treatment with favipiravir in the face of COVID-19 is clearly in favor of potential study subjects.

This study will assess the time course of cessation of viral shedding and gather clinical benefit information in subjects with COVID-19 treated with favipiravir as compared to control. Data from this trial are expected to support the planning and execution of a larger study to demonstrate clinical benefit. The information gathered from this study will also help define the safety profile of favipiravir during the global pandemic and enable expansion into other subject populations such as those who have been exposed but who are not yet ill.

1.1.2. Study Objectives

The primary objective of this study is to determine the effect of favipiravir plus standard of care (SOC) vs SOC on viral clearance.

The secondary objectives of the study are as follows:

- To determine the clinical benefit of administering favipiravir plus SOC compared to SOC alone (assessed using a study-specified 6-point ordinal scale adapted from the

World Health Organization [WHO] Master Protocol [V2.0 24FEB20] COVID-19 7-point ordinal scale) in adult subjects hospitalized with COVID-19.

- To determine if the treatment effect on the 6-point ordinal scale, on Day 15, is reasonably likely to reflect clinical benefit such that it can be used as the primary clinical outcome endpoint in a similar study that is double-blinded, by assessment of the relationship of the scale to changes in clinical and symptom outcomes, including time to clinical recovery, occurrence of fever, cough, dyspnea, reduction in oxygen requirements, and other measures.
- To explore the clinical effect of favipiravir + SOC vs SOC as measured by the National Early Warning Score 2 (NEWS2) system.
- To determine the safety of favipiravir plus SOC compared to SOC alone in this population.
- To explore the pharmacokinetics (PK) of this dose regimen of favipiravir in this subject population.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2. Study Design

1.2.1. Synopsis of Study Design

This study is an open label, randomized, SOC-controlled, multicenter Phase 2 study of favipiravir in hospitalized subjects with COVID-19. Subjects will be randomized within their study site and stratified by the severity of disease to receive either favipiravir + SOC or SOC alone.

Standard of care will be site-specific and based on what each site is currently using for treatment of hospitalized COVID-19 patients.

The dose regimen will be 1800 mg favipiravir twice daily (BID) plus SOC or SOC alone on Day 1 followed by 1000 mg BID favipiravir (800 mg BID for subjects with Child-Pugh A liver impairment) plus SOC or SOC for the next 13 days.

Subjects are planned to have 14 days of treatment and 46 days of follow-up.

1.2.2. Randomization Methodology

Subjects will be evaluated for eligibility during Day 1, prior enrollment in the study or starting treatment. The randomization procedure will be performed centrally using the electronic data capture (EDC) system, IBM Clinical Development.

Approximately 50 subjects are planned to be randomized at a 1:1 ratio to receive either favipiravir + SOC or SOC alone. Randomization will be stratified by site and severity of illness at enrollment. Severity of illness at enrollment will be graded (i.e., critical disease, severe disease, or mild//moderate disease) as follows:

- Critical disease:
  - Requires supplemental oxygen delivered by non-rebreather mask or high-flow cannula, OR
  - Requires use of invasive or non-invasive ventilation, OR
  - Requires treatment in an intensive care unit, use of vasopressors, extracorporeal life support (i.e., extracorporeal membrane oxygenation [ECMO]).
- Severe disease:
  - Evidence of pneumonia on chest x-ray or computed tomography (CT) scan, or chest auscultation (rales, crackles), OR
  - Peripheral capillary oxygen saturation (SpO_2) ≤ 93% on room air OR partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) < 300 mmHg, OR
  - Requires supplemental oxygen by nasal canula, simple face mask, or other similar oxygen delivery device.
- Mild/moderate disease: SpO_2 > 94% and respiratory rate ≤ 24 breaths/min without supplemental oxygen

The randomization will target balance within stratum. This does not guarantee balance overall; however, utilizing a block size of 2, as well as with sufficient sample size within strata, balance will be approximately maintained while pooling across sites.

1.2.3. Removal of Subjects from Treatment

The participation of a subject in the study or the administration of treatment may be terminated at any time for one of the following reasons:

- The subject desires to discontinue study treatment.
- The subject withdraws consent to participate in the study.
- The subject is unwilling or unable to comply with the safety procedures.
- The subject is discovered to be pregnant.
- The subject experiences a medical emergency that necessitates withdrawal.

- The subject is withdrawn at the discretion of the Investigator for medical reasons or non-compliance.

1.2.4. Stopping Rules

A subject should be removed from favipiravir treatment if one of the following criteria is met:

- Alanine transaminase (ALT) or aspartate transaminase (AST) > 8 × upper limit of normal (ULN)
- ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN
- ALT or AST > 3 × ULN AND subject has right upper quadrant pain or eosinophilia
- Uric acid >20 mg/dL

A subject whose treatment is terminated should remain in the study for appropriate follow-up assessments.

1.2.5. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1.

Table 1-1 Schedule of Assessments

ASSESSMENT	HOSPITALIZED							FOLLOW-UP Outsubject or Hospitalized		
	DAY 1 PRE-DOSE	DAY 1 POST-DOSE	DAY 2	DAY 3	DAY 8	Day 11	DAY 14	DAY 15 + (-1 to + up to 2 days	DAY 29 ± 2 days	DAY 45 and 60 ± 2 days[8]
Informed Consent	X									
Medical/Surgical History	X									
Physical Exam[10]	X									
Limited Physical Exam[3]		X	X	X	X	X	X	X	X	X
Concomitant Medications Review[12]	X		X	X	X	X	X	X	X	X
Review of Entry Criteria	X									
Vital Signs (BP, HR, Temp, Resp)[3]	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Exams[1,2,9]	X			X	X	X		X	X	
Blood for antibodies to SARS-CoV-2	X							X	X	
Blood for PK Sampling	X[4]	X[4]	X[5]	X[6]	X[5]	X[6]	X[5]			
SpO_2 by Finger Sensor[3]	X	X	X	X	X	X	X	X	X	X
Urine or Blood Pregnancy Test	X									
Nasopharyngeal and Oropharyngeal Swabs for Viral RNA, PCR	X			X[11]	X[11]	X[11]		X	X	

ASSESSMENT	**HOSPITALIZED**							**FOLLOW-UP Outsubject or Hospitalized**		
	DAY 1 PRE-DOSE	**DAY 1 POST-DOSE**	**DAY 2**	**DAY 3**	**DAY 8**	**Day 11**	**DAY 14**	**DAY 15 + (-1 to + up to 2 days**	**DAY 29 ± 2 days**	**DAY 45 and 60 ± 2 days[8]**
and $TCID_{50}$										
Clinical Status – 6-point Ordinal Scale[3]	X		X	X	X	X		X	X	X
National Early Warning Score (NEWS2)[3]	X		X	X	X	X		X	X	X
ECOG Performance Status[3]	X		X	X	X	X	X	X	X	X
Study Specific Symptom Status[3]	X		X	X	X	X	X	X	X	X
Randomization	X									
Investigational Product Dosing		Favipiravir Dosing Days 1-14 (1800mg BID on Day 1000mg BID Days 2-14)[7]								
Solicitation of Treatment-Emergent Adverse Events[3]		X	X	X	X	X	X	X	X	X
Release from the Study										X

1. Hematology, Chemistry (See Protocol Section 8.4).
2. May use results of labs taken at the hospital as part of SOC if done no more than 24 hours prior.
3. To be measured every day while hospitalized and at each clinic visit after hospital discharge through Day 60
    a. Vital signs
    b. Clinical Status 6-point scale
    c. NEWS2
    d. ECOG Performance status
    e. Study-specific symptom status
    f. Adverse Events
    g. SpO_2
    h. Limited PE (heart and lungs)
4. PK on Day 1 prior to favipiravir dosing and between 45 to 75 minutes post-first dose.

5. PK trough samples to be taken approximately 30 minutes prior to any dose.
6. PK peak samples to be taken between 45 and 75 minutes post-dose.
7. Maintenance dose for CP score A is 800mg BID.
8. Days 45 and 60 may be completed in the hospital, outsubject clinic or by phone.
9. Subjects will undergo 9 planned venipunctures.
10. To be completed by PI or designee.
11. Days 3, 8, 11 Nasopharyngeal and Oropharyngeal Swabs for Viral RNA, PCR, and TCID50 may be done +/- 1 day from their scheduled day. Swabs will also be obtained on day of discharge from hospital if discharge occurs before Day 15.
12. To be checked throughout hospitalization and at clinic visits and changes only recorded as applicable.

1.2.6. Efficacy, Pharmacokinetic, and Safety Parameters

1.2.6.1. Efficacy Parameters

Efficacy will be measured through the following parameters:

For Primary Endpoint:

- PCR in the nasopharyngeal and oropharyngeal samples taken on Days 1, 3, 8, 11, 15 and 29. Swabs will also be obtained on day of discharge from hospital if discharge occurs before Day 15.

For Secondary Endpoint:

- Clinical improvement of hospitalized subjects with COVID-19 receiving either favipiravir + SOC or SOC alone as defined by the following study-specific 6-point ordinal scale assessed daily while hospitalized and at each outpatient visit until Day 60..
  1. Not hospitalized
  2. Hospitalized, not requiring supplemental oxygen
  3. Hospitalized, requiring supplemental oxygen
  4. Hospitalized, on non-invasive ventilation or high flow oxygen devices
  5. Hospitalized, on invasive mechanical ventilation or ECMO
  6. Death
- NEWS2 assessed daily while hospitalized and at each outpatient visit until Day 60.
- Vital signs (BP, HR, RR, BT, SpO_2) measured daily while hospitalized and at each outpatient visit until Day 60.
- Patient status assessed daily while hospitalized and at each outpatient visit until Day 60 via Study-specific Symptom Status and ECOG Performance Status questionnaires
- Period of each respiratory assistance (if applicable).
- Period of hospitalization.
- Period of intensive care unit (if applicable).
- Date and cause of death (if applicable).
- TCID50 in nasopharyngeal and oropharyngeal swabs on Days 1, 3, 8, 11, 15 and 29. Swabs will also be obtained on day of discharge from hospital if discharge occurs before Day 15.

  Note: Since TCID50 for SARS-CoV-2 is not yet proven to be sensitive for detection of the virus and is still under development for that purpose, analyses using TCID50 will not be conducted if TCID50 for SARS-CoV-2 is not detectable enough.

- Blood for determination of antibodies to SARS-CoV-2 obtained on Days 1, 15 and 29.

1.2.6.2. Pharmacokinetic Parameters

The PK measurement in blood samples taken on Days 1, 2, 3, 8, 11 and 14.

1.2.6.3. Safety Parameters

Abnormal clinical laboratory values that are clinically significant and all reported adverse events (AEs) will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Safety will be assessed by the following:

- Observed and reported AEs (including solicited and unsolicited events)
- Hematology and chemistry laboratories on Days 1, 3, 5, 8, 11, 15 and 29; if coagulation laboratory assays are ordered as part of the SOC, the results will be recorded
- Limited physical examination assessed daily while hospitalized and at each outpatient visit until Day 60.

2. SUBJECT POPULATION

2.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-treat (ITT) population – All subjects randomized to treatment. Subjects in the ITT population will be analyzed based on the treatment to which they were randomized, irrespective of what treatment they actually received. This population was selected for the analysis of the primary and secondary endpoints in order to maintain the benefits of randomization and avoid the potential bias associated with the non-random loss of the participant.

- Safety population – All ITT subjects who received either favipiravir + SOC or SOC alone. Subjects in the safety population will be analyzed based on the actual treatment they received, irrespective of the treatment to which they were randomized. It is anticipated that the safety population will be the same as the ITT population.

- Modified intent-to-treat (mITT) – All subjects of the ITT population that have a post-baseline assessment of viral shedding and at least one PCR positive result for SARS-CoV-2 in any protocol-required swab samples. Note that results recorded as less than the lower limit of quantification (LLOQ) are considered to be negative. Subjects in the mITT population will be analyzed based on the treatment to which they were randomized, irrespective of what treatment they actually received.

- Per protocol (PP) population – All mITT subjects who adhere to relevant study procedures (i.e. have no major protocol deviation that would be expected to affect efficacy assessments) and have an outcome assessment.

- PK population (PK) – All subjects in the safety population that have at least one result that can be used in the PK summaries.

The ITT population is the primary population for the analysis of efficacy parameters; the mITT and PP populations will be used for supportive inferences concerning efficacy. The PK population is the primary population for the analysis of PK parameters. The Safety population is the primary population for the analysis of safety endpoints.

2.2. Protocol Violations

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Approximately 50 subjects will be enrolled. The primary endpoint analysis will consist of a log-rank test of the difference in treatment groups in the time to viral clearance. Based on a recent publication

(https://www.sciencedirect.com/science/article/pii/S2095809920300631?via%3Dihub),

it is assumed that the median time to clearance for favipiravir would be approximately 4 days, and the median time for placebo would likely be approximately 11 days. This latter estimate may be conservative since SOC is not as likely to reduce viral load as well as the control in the above referenced study. Using two-sided alpha of 0.10 and power of 90% (appropriate for a trial to be used as the justification for a confirmatory, fully-powered, blinded and randomized Phase 3 study), and a fixed per-subject observation period of 15 days, an approximate sample size of 25 subjects per arm (total size of 50) is required.

3.2. Efficacy Endpoints and Hypothesis Testing

The primary efficacy endpoint is time to viral clearance by PCR, measured on Days 1, 3, 8, 11 (while hospitalized); and days 15 and 29 (if able to return to clinic or still hospitalized).

Contrary to what is included in the study protocol, the hierarchical testing of key secondary endpoints will not be performed. For more information please refer to Section 5.

All analyses will be conducted at the two-sided alpha-level of 0.10. P-values for all analyses other than the primary efficacy endpoint will be presented for the purposes of 'descriptive significance' only.

3.3. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word, or Adobe Acrobat PDF files, sorted and labeled according to the International Council for Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, PK, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented along with 2-sided 90% confidence intervals (CIs). For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented, as well as 2-sided 90% CIs. Time-to-event data will be summarized using Kaplan-Meier methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-

sided 90% CIs, as well as percentage of censored observations. Where appropriate, p-values will be reported.

Assuming raw or derived variables are to 'x' decimal places, the data will be presented as follows:

- Range to x decimal places
- Mean and median to (x+1) decimal places
- SD to (x+2) decimal places
- (x+2) should not be greater than 4 decimal places
- percentages may be calculated without a decimal place or with (x+1) decimal place

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints as described in Section 4 with all tests conducted at the 2-sided, 0.10 level of significance.

Data will be presented by subject and summarized by treatment group.

3.4. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Concomitant medications will be coded using the WHO Drug Dictionary Version March 2020.

3.5. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug for patients on favipiravir. For patients on SOC, baseline will be defined as the closest (either before or after) measurement to randomization.

For the purpose of time-to-event analyses, treatment start date is used as the origin point for patients on favipiravir, while randomization date is used for patients on SOC.

3.6. Methods of Pooling Data

Efficacy data will be pooled across study sites for analysis.

3.7. Adjustments for Covariates

For the analyses of durations of supplemental oxygen, non-invasive/mechanical ventilation, Extracorporeal Membrane Oxygenation (ECMO), hospitalization, and ICU, baseline SpO_2 level will act as a covariate in all analysis of covariance (ANCOVA) models. Disease severity, as defined in Section 1.2.2, will be accounted for in all efficacy analyses. Other factors may be accounted for if deemed relevant.

3.8. Subpopulations

Subgroup analyses on dexamethasone usage (Yes/No) will be performed on the primary efficacy analyses, as well as on select secondary efficacy analyses. Other subgroups of interest may be analyzed for exploratory purposes.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

3.10.1. Efficacy Data

Should missing data occur for time-to-event endpoints, such subjects will be included in the log-rank analysis as censored observations as specified in Section 4.3.1.

Missing clinical outcome data for secondary efficacy endpoints (other than time-to-event) will be handled by a multiple imputation model that contains the following variables: baseline and post-baseline parameter values, and disease severity, stratified by treatment group. Imputation of missing data will be conducted under a working assumption of missing at random (MAR), meaning that the propensity for a data point to be missing is not related to the missing data, but it is related to some of the observed data.

The imputations will be performed for post-baseline visits. The Fully Conditional Specification (FCS) method will be used, given its natural handling of both ordinal and nominal variables (Liu & De 2015). Predicted Mean Matching (PMM) (using a linear prediction model to obtain predicted values and k=5 for randomly drawing from k^{th} nearest observed values to the predicted value) will be implemented under FCS (Schenker & Taylor 1996). One hundred (100) datasets will be imputed in order to estimate the treatment effect, where the median value across the imputed datasets will be used for subjects with missing endpoints.

3.10.2. Adverse Event Data

When tabulating AE data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the onset day to the date of the first dose.
- If the month and day are missing, and the year is:
    - the same as the year of first dose, then set the onset day as the first day of the month of the first dose;
    - earlier than the year of first dose, then set the onset day as December 31;
    - after the year of the first dose, then set the onset day as January 1.

- If only the day is missing, then
    - if the month/year is the same as the first dose, then set the onset day as the date of first dose;
    - if the month/year is earlier than the month/year of the first dose, then set the onset day as the last day of the month;
    - if the month/year is later than the month/year of the first dose, then set the onset day as the first day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing, and the year is the same as the year of the last dose then set the end day as the last day of the month of the first dose. Otherwise, set the end date as December 31.
- If only the day is missing, then set the end day as the last day of the month.

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

3.10.3. Prior and Concomitant Medication

When tabulating prior/concomitant medication data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the start date to the date of first dose.
- If the month and day are missing and the year is earlier than the year of the first dose, then set the start date to December 31. Otherwise, set the start date to January 1.
- If only the day is missing, if the month/year is earlier than the month/year of the first dose then set the start date to the first day of the month. Otherwise, set the start date to the last day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing then set the end date to December 31.
- If only the day is missing, then set the end day as the last day of the month.

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. However, analysis visits will be derived based on study day for all by-visit summaries and analyses. Analysis visit designations are detailed in Table 3-1.

Table 3-1 Post-Baseline Analysis Visit Designations

Analysis Visit	Analysis Visit Range
Day 1	Day 1
Day 2	Day 2
Day 3	Days 3-5
Day 8	Days 6-9
Day 11	Days 10-12
Day 15	Days 13-17
Day 21	Days 18-24
Day 29	Days 25-33
Day 45	Days 34-52
Day 60	Days 53-70

In the event there are multiple assessments within a given analysis range, the value closest to the target day (understood to be the day identified in the analysis visit) will be chosen. If more than one measurement are the same distance from the target day, the earlier visit will be chosen.

In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

No interim analyses are planned for this study.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated by treatment group and include the number randomized, the number treated, the number in each population for analysis, and the number who completed the treatment (who reached Day 14 for SOC alone), the number who completed the study (i.e., reached Day 29 visit), and the number who discontinued treatment and discontinued study and reason(s) for withdrawal.

A by-subject data listing of treatment and study completion information including the reason for treatment discontinuation and study discontinuation, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be tabulated by treatment group. Age (years), race, gender, ethnicity, and smoking status use will be summarized using descriptive statistics. In addition, the number of subjects with Child-Pugh A liver impairment, and the number of patients who received a bacillus Calmette-Guérin (BCG) vaccine will be provided. Baseline disease characteristics will also be summarized; these include the number of subjects in each stratification level (based on disease severity), the number of subjects who require each type of respiratory assistance, the number of subjects who had antibodies to SARS-CoV-2 at baseline, SpO_2 at baseline, and days from symptom onset, from PCR positivity, and from start of hospitalization to randomization. Demographic and baseline data for each subject will be provided in data listings.

Medical history will be coded using MedDRA v23.0 and presented by system organ class and preferred term by treatment group. If a subject had more than one medical history event within a system organ class, the subject is counted once for each preferred term and once for the system organ class. Medical history data will also be provided in by-subject listings.

Demographic and baseline characteristics summary tabulations will be produced for the ITT population.

4.3. Efficacy Evaluation

4.3.1. Analysis of the Primary Efficacy Endpoint

The primary endpoint of time to viral clearance will be analyzed with the log-rank test for treatment difference based on a two-sided alpha-level of 0.10 and summarized using Kaplan-Meier methodology. The time to viral clearance (in days) is defined as the time of Negative or Lower Limit of Quantification (LLOQ) results (without any quantitative results after that) as measured by PCR for SARS-CoV-2 via scheduled nasopharyngeal and oropharyngeal swab samples minus the date of first dose + 1.

Subjects who have no evidence of viral clearance will be censored at the time of the last PCR measurement with the following conditions:

- Patients whose symptoms worsen (defined as an increase of ≥ 1 point on the 6-point Ordinal Scale from baseline) on the day of the last PCR measurement, or who die will be censored at Day 29,

- Patients who are lost to follow-up will be censored on the day of the last PCR measurement.

The median time to viral clearance will be estimated based on the Kaplan-Meier estimator; additional summary statistics will be presented, including the 25th and 75th percentiles, 90% CIs (the log-log transformation) on the median and other percentiles and proportion of censored subjects. Viral clearance rates at Days 3, 8, 11, 15, and 29 will also be presented.

The analysis of the primary efficacy endpoint will be done using the ITT population.

The primary analysis will be supplemented with a sensitivity analysis, using a stratified log-rank test, where the treatment difference based on a two-sided alpha-level of 0.10 will be summarized and stratified by disease severity.

The analysis will also be repeated by the dexamethasone usage subgroup, where patients will be categorized as having received dexamethasone if they received it at any time prior to the last viral clearance assessment.

Kaplan-Meier curves will be provided for the overall ITT population. By-subject data listings of viral clearance data will also be provided.

4.3.2. Analysis of Secondary Efficacy Endpoints

4.3.2.1. Analysis of Clinical Status via the Study-Specific 6-point Ordinal Scale

The first secondary endpoint of clinical status as measured by the study-specific 6-point ordinal scale at Day 15 will be analyzed by fitting a cumulative odds model, using the most appropriate approach. Clinical status will be modelled as the dependent variable (ordered from 1 to 6, as defined in Section 1.2.6.1), and treatment group and disease severity as independent variables; other factors may be added for exploratory purposes. Subjects with missing Day 15 data will have their clinical status imputed in the following manner:

1) If patients were discharged prior to Day 15, then their clinical status will be imputed to 'Not Hospitalized' at Day 15
2) If patients died prior to Day 15, then their clinical status will be imputed to 'Death' at Day 15
3) If there is no evidence of hospital discharge or death, clinical status at Day 15 will be imputed using the multiple imputation method described in Section 3.10.1

The odds ratios and their 90% CI will be provided. As described in Section 3.2, a test at the two-sided alpha level of 0.10 will be performed for descriptive purposes.

Longitudinal analysis of the 6-point scale over time at each visit will be performed in a similar manner. Clinical status will be modelled as the dependent variable and treatment group, disease severity, visit, and the visit/treatment group interaction term as independent variables. The overall treatment odds ratio and their 90% CI will be provided, along with by-visit odds ratios and 90% CI.

Analyses using the study-specific 6-point scale will be done using the ITT population.

The analysis will also be repeated by the dexamethasone usage subgroup, where patients will be categorized as having received dexamethasone if they received it at any time prior the Day 15 analysis visit assessment.

Stacked bar charts over time will be generated to graphically display the proportion of patients in each level of the 6-point scale by treatment group for the ITT population.

By-subject data listings will be provided.

4.3.2.1.1. Sensitivity Analysis

The following sensitivity analyses are planned for supportive inference using the ITT population:

1) The status of clinical recovery at Day 15 analysis will be repeated using the single imputation method of Last Observation Carried Forward (LOCF) rather than the multiple imputation approach described in Section 3.10.1

2) Clinical status will be dichotomized over time, where subjects will be classified as either improved (Yes) or declined/no change (No) based on the 6-point scale result from the baseline visit. Subjects who are discharged or deceased over time will not contribute to subsequent timepoints. The treatment effect will be analyzed via generalized linear mixed models using SAS PROC GLIMMIX, with improvement in clinical status (yes/no) as the dependent variable, and treatment group, disease severity, and visit as independent variables. Least-squares means of the treatment group effect on the logit scale (difference on the log odds) will be utilized for analysis, where the odds ratio and corresponding 90% CI will be provided

4.3.2.2. Time to Clinical Recovery

The time to clinical recovery (TTCR) assessed up to 29 days will be analyzed in a similar manner as the primary efficacy endpoint. TTCR is defined as the time (in days) from initiation of study treatment (favipiravir + SOC or SOC alone) until normalization of fever, respiratory rate, oxygen saturation, and alleviation of cough, sustained for at least 72 hours; or hospital discharge. The normalization and alleviation criteria are presented in Table 4-1.

Table 4-1 Normalization and Alleviation Criteria

Parameter	Criteria
Fever	≤37.2 ºC
Respiratory Rate	≤24 breaths/minute on room air
Oxygen Saturation	SpO_2 > 94% on room air
Cough	Mild or absent on a subject-reported scale of severe, moderate, mild, absent

Subjects with no evidence of clinical recovery will be censored at last assessment of the parameter that is not be recovered. The censoring rules as provided in Section 4.3.1 will also be employed. In addition, if a subject achieves TTCR and then discontinues from the study during the 72 hour confirmation period, it will be censored at the discontinuation. If a subject achieves TTCR and then discharge, it will be confirmed as recovered at the time of achieving TTCR.

The difference between treatment groups will be analyzed using a log-rank test at the two-sided alpha level of 0.10, where the p-value will be presented for descriptive purposes (and using a stratified log-rank test by disease severity as a sensitivity analysis).

Analyses of TTCR will be done on the ITT population. Only patients with at least one abnormal result (among the four symptoms listed in Table 4-1) at baseline (or within 72 hours post baseline) will be included in the analysis.

Kaplan-Meier curves will be provided for the overall ITT population. By-subject data listings will also be provided.

In addition, the analysis will be performed with stratification by disease severity.

The analysis will also be repeated by the dexamethasone usage subgroup, where patients will be categorized as having received dexamethasone if they received it at any time prior to the last assessments of normalization and alleviation criteria.

4.3.2.3. Progression/Reduction in Disease Symptoms

All the analyses below will be done on the ITT population with the same methodology as the analysis of time to clinical recovery in Section 4.3.2.2.

The analyses of time to defervescence, mild/absent cough, and mild/absent dyspnea will also be performed stratified by disease severity.

In addition to the specified analyses, all data will be provided via by-subject data listings.

4.3.2.3.1. Respiratory Progression

The frequency of respiratory progression as assessed up to Day 29 will be tabulated by treatment group. Respiratory progression is defined as:

SpO_2 ≤94% on room air or PaO_2/FiO_2 < 300 mmHg, and

a. Requirement for supplemental oxygen, or
b. More advanced ventilator support

The treatment effect will be analyzed via generalized linear mixed models using SAS PROC GLIMMIX, with respiratory progression (Yes/No) as the dependent variable, and treatment group, disease severity, age (in years), and visit as independent variables. Least-squares means of the treatment group effect on the logit scale (difference on the log odds) will be presented, along with a 90% CI and a descriptive p-value from a two-sided alpha-level test.

4.3.2.3.2. Time to Defervescence

Summary statistics of time to defervescence assessed up to 29 days, if possible, will be presented by treatment group. Time to defervescence is defined as the time (in days) from initiation of study treatment (favipiravir + SOC or SOC alone) until normalization of fever, described as an oral temperature ≤37.2 ºC, or discharge. Only subjects with fever at study entry or within the first 72 hours will contribute to this analysis.

A Kaplan-Meier curve will be provided for the overall ITT population, where subjects will be censored at the last assessment of the parameter if no defervescence is observed.

4.3.2.3.3. Time to Mild/Absent Cough

Time to mild/absent cough will be analyzed in a similar fashion to time to defervescence. Only subjects with reported moderate or severe cough at study entry or within the first 72 hours will contribute to this analysis. Subjects will be censored at the last assessment of the parameter if no mild/absent cough is observed.

4.3.2.3.4. Time to Mild/Absent Dyspnea

Time to mild/absent dyspnea will be analyzed in a similar fashion to time to defervescence. Only subjects with reported moderate or severe dyspnea at study entry or within the first 72 hours will contribute to this analysis. Subjects will be censored at the last assessment of the parameter if no mild/absent dyspnea is observed.

4.3.2.3.5. ECOG Performance Status

ECOG performance status will be tabulated over time by treatment group.

4.3.2.4. Analysis of the National Early Warning Score

The time to aggregate NEWS2 score of ≤ 2 (sustained for at least 72 hours) or hospital discharge will be analyzed up to Day 29 in a similar manner as the time to TTCR described in Section 4.3.2.2. Only patients with a score >2 at baseline or within 72 hours post baseline will contribute to the analysis. Subjects will be censored at last assessment of the parameter if there are no events of ≤ 2 aggregate scores. The censoring rules as provided in Section 4.3.1 will also be employed. In addition, if a subject achieves the event and then discontinues from the study

during the 72-hour confirmation period, it will be censored at the discontinuation. If a subject achieves the event and then discharge, it will be confirmed as reach the event at the time of aggregate NEWS2 score of ≤ 2; Kaplan-Meier curves will be provided for the overall ITT population.

In addition, the analysis will be performed with stratification by disease severity.

Additionally, descriptive statistics of mean changes from baseline in aggregate NEWS2 scores to post-baseline visits will be provided by treatment group. This analysis will be performed using the ITT population. Only patients with at least one-post baseline measurement will be included.

By-subject data listings will be provided.

4.3.2.5. Reduction in Oxygen/Ventilation Requirements

The frequency of requirement for any supplemental oxygen or ventilation (non-invasive, mechanical, or ECMO), as assessed daily up to 29 days and on Day 45 and 60, if possible, will be analyzed in a similar fashion as respiratory progression in Section 4.3.2.3.1.

In addition, the frequency of requirement for any ventilation requirement (non-invasive, mechanical or ECMO) and either mechanical ventilation or ECMO will be analyzed in the same manner as above.

The analyses on oxygen/ventilation requirements will be performed using the ITT population.

4.3.2.6. Duration of Supplemental Oxygen, Non-Invasive Ventilation, Mechanical Ventilation, ECMO, Hospitalization, and Time in ICU

The total duration (in days) of any respiratory assistance (supplemental oxygen, non-invasive ventilation, mechanical ventilation, ECMO), hospitalization, and ICU will be analyzed using an ANCOVA model, investigating the difference in means between the treatment groups. The difference in mean durations between treatment groups will be provided, along with 90% CI. All durations are counted from randomization. In addition, the total time on any ventilation assistance (non-invasive/mechanical ventilation, ECMO), and either mechanical ventilation or ECMO will be analyzed using an ANCOVA model as above.

The exact duration will be counted. But, it was initiated prior to study enrollment, duration will be calculated from treatment start date for patients on favipiravir and randomization date for patients on SOC. The maximum value of these durations will not exceed 60 days

The analyses above will be performed using the ITT population.

Box plots for the total duration of any respiratory assistance and hospitalization will be provided by treatment group. By-subject data listings for each parameter will also be provided.

4.3.2.7. All-Cause Mortality

All-cause mortality will be analyzed by investigating the relationship between all-cause mortality and treatment group. An adjusted relative risk analysis will be done using a stratified Cochran-Mantel-Haenszel test; the cross-tabulation of all-cause mortality and treatment group will be stratified by disease severity. The adjusted relative risk will be provided, along with a 90% CI.

All-cause mortality will be analyzed using the ITT population.

A by-subject data listing will be provided.

4.3.2.8. Time to SARS-CoV-2 TCID50 Negative

Time to SARS-CoV-2 TCID50 negative in upper respiratory tract will be analyzed in a similar fashion as the primary efficacy endpoint. Time to SARS-CoV-2 TCID50 negative is defined as the time (in days) from initiation of study treatment (favipiravir + SOC or SOC alone) until a negative assessment in upper respiratory tract specimen.

Time to SARS-CoV-2 TCID50 negative will be performed on the mITT population.

Note: Since TCID50 for SARS-CoV-2 is not yet proven to be sensitive for detection of the virus and is still under development for that purpose, analyses using TCID50 will not be conducted if TCID50 for SARS-CoV-2 is not detectable enough.

4.3.2.9. Change in SARS-CoV-2 Viral Load

The change in SARS-CoV-2 viral load in upper respiratory tract specimen as assessed by area under viral load curve (quantitative PCR) as assessed up to 29 days. The area under the curve (AUC) over time for a given subject will be calculated, using the linear trapezoidal rule, as the sum of the maximum viral load for each day up through Day 29. Lower Limit of Quantification (LLOQ) result is considered as negative. An analysis of treatment group differences will be performed on the change in viral load using ANOVA model, with treatment group and disease severity as fixed factors.

The change in SARS-CoV-2 viral load will be analyzed by comparing the change between treatment groups using a mixed model with repeated measures (MMRM). This analysis will assess whether or not there is a difference in estimated change from baseline values between active treatment and SOC by visit using least squares means estimates from the MMRM.SAS PROC MIXED will be used to fit an MMRM with change from baseline in SARS-CoV-2 viral load as the response variable and the following covariates and fixed effects:

- Baseline SARS-CoV-2 viral load (covariate)
- Treatment group (fixed effect)
- Visit (fixed effect, time will be defined in terms of Visits)
- Time by Treatment Interaction (Time*Treatment)

The covariance structure for the repeated measures in this model will be unstructured (UN). If UN does not converge for the model, a first-order autoregressive (AR(1)) covariance structure will be used.

Changes in viral load will be analyzed using the mITT population.

By-subject data listings will also be provided.

4.3.2.10. Neutralizing Antibodies

Summaries of neutralizing antibody titers will be presented over time by treatment group using descriptive statistics. Antibody titer results will be summarized for each dilution at which 50% neutralization was observed.

The analysis of antibody titers will be performed using the ITT populations.

By-subject data listings will also be provided.

4.4. Pharmacokinetic Evaluations

All PK data analysis will be conducted using the PK population.

Maximum plasma concentration (Cmax), minimum plasma concentration (Cmin), and AUC(0-24h) on Days 1, 2, 3, 8, 11 and 14 will be calculated. Plasma PK parameters will be summarized and plotted using descriptive statistics, as appropriate.

4.5. Safety Analyses

Safety analyses will be conducted using the Safety population.

4.5.1. Study Drug Exposure

Duration of study drug exposure will be calculated as the number of days subjects were administered study drug and will be summarized for the favipiravir arm using descriptive statistics.

Total drug received (in mg) will be summarized for the favipiravir arm. Percent compliance will be summarized for each subject from the date of first dose through the last dose of study drug per the following definition:

$$Percent\ Compliance\ (\%) = \frac{Actual\ cumulative\ amount\ of\ drug\ received\ (mg)}{Planned\ cumulative\ amount\ of\ drug\ received\ (mg)} \times 100\%$$

For subjects who withdrew/discontinued treatment prematurely, the amount of drug planned will be calculated based on the period of treatment up to their withdrawal/termination.

Each Study drug administration per patient will be provided in data listings.

4.5.2. Adverse Events

All AEs will be coded using the MedDRA v23.0 coding system and displayed in tables and data listings using system organ class and preferred term. Missing and partial dates will be handled as described in Section 3.10.2.

Treatment-emergent AEs (TEAEs) will be defined as those occurring coincident with start of treatment through Day 60.

In the favipiravir + SOC arm: Adverse event solicitation and recording will begin immediately following the first dose of favipiravir and will include only on-treatment (treatment-emergent) events. Any changes to a subject's health that occur between the signing of the informed consent and dosing will be recorded as updates to the subject's medical history.

In the SOC alone arm: Adverse event solicitation and recording will begin following the completion of all baseline assessments.

Clinical events related to the progression of COVID-19 will **not** be considered AEs.

Adverse events are summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given AE in both SOC and preferred term.

The number and percentage of patients with any TEAE, with any TEAE assessed by the Investigator as related to treatment, with any serious TEAE, and with any treatment-emergent serious AE (SAE) potentially related to treatment will be summarized by treatment group and overall.

All AEs occurring on-study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths, SAEs, and AEs leading to treatment/study discontinuation.

4.5.3. Laboratory Data

Clinical laboratory values will be expressed in SI units.

All laboratory data will be provided in data listings.

Abnormal clinical laboratory values that are clinically significant will be graded according to the CTCAE version 5.0. A listing of all abnormal laboratory values will be provided.

Shift tables for hematology and chemistry parameters from baseline to worst value will be provided by treatment group and overall. All unscheduled visits, if any, will contribute to the last or worst value.

4.5.4. Vital Signs and Physical Examination

The actual values and changes from baseline to each on-study evaluation will be summarized for vital signs by treatment group and overall.

Vital sign measurements will be presented for each subject in a data listing.

4.5.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary.

The use of prior and concomitant medications will be included in a by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

The following are changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan:

- The hierarchical testing of the key secondary endpoints has been removed, given that this study is a Proof of Concept study that is not meant to act as a pivotal or confirmatory study for marketing authorization.

All changes from procedures outlined in the protocol and procedures outlined in this SAP will be summarized in the study report. Decisions to deviate from planned analyses will be documented at the time they are made.

6. REFERENCES

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Schenker, N., and Taylor, J. M. G. (1996). "Partially Parametric Techniques for Multiple Imputation." *Computational Statistics and Data Analysis* 22:425–446