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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INVESTIGATIONAL PRODUCT:	favipiravir
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SPONSORED BY:	FUJIFILM Pharmaceuticals U.S.A., Inc. One Broadway, Cambridge, MA 02142 USA
CONTACT INFORMATION:	[redacted]

FUJIFILM PHARMACEUTICALS U.S.A., INC.
PROTOCOL FAVI-COV-US201 APPROVAL

Version 6.0, 15July2020

(SIGNATURES ON FILE AT FPHU)

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PROTOCOL SIGNATURE PAGE

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

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____
Date (MM/DD/YYYY)

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AO	Aldehyde oxidase
AST	Aspartate aminotransferase
BID	“bis in dies” / Twice a day
BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence interval(s)
COVID-19	Corona Virus Disease 2019
CRP	C-reactive Protein
EC_{50}	Half maximal effective concentration
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
FiO2	Fraction of inspired oxygen
FPHU	FUJIFILM Pharmaceuticals U.S.A., Inc.
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Institutional ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intra-uterine device
MedDRA	Medical dictionary for regulatory activities
MERS-CoV	Middle East respiratory syndrome coronavirus
MITT	Modified intent-to-treat
NEWS2	National early warning score 2

NO	Nitrous Oxide
PaO2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per-protocol
RNA	Ribo-nucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome corona virus 2
SD	Standard deviation
SOC	Standard of care
SpO2	Peripheral capillary oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
$TCID_{50}$	Median tissue culture infectious dose
TEAE	Treatment-emergent adverse event
TTCR	Time to clinical recovery
WHO	World Health Organization

1 SYNOPSIS

Title	Open Label, Randomized, Controlled, Phase 2 Proof-of-Concept Study of the Use of Favipiravir v. Standard of Care in Hospitalized Subjects with COVID-19
Design	This is an open label, randomized, controlled, multicenter Phase 2 proof-of-concept study of favipiravir in hospitalized subjects with COVID-19. Subjects will be randomized within their study site and stratified by the severity of their disease to receive either favipiravir + standard of care (SOC) or SOC alone. The dose regimen will be 1800 mg favipiravir 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. The study will have 14 days of treatment and 46 days of follow-up.
Objectives	**Primary Objective** To determine the effect of favipiravir + SOC v. SOC on viral clearance. **Secondary Objectives** 1. To determine the clinical benefit of administering favipiravir plus SOC compared to SOC alone [assessed using a study-specific 6-point ordinal scale adapted from the WHO Master Protocol (V2.0 24FEB20) COVID-19 7-point ordinal scale] on Day 15 in adult patients hospitalized with COVID-19. 2. 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. 3. To explore the clinical effect of favipiravir + SOC v. SOC as measured by the National Early Warning Score 2 (NEWS2) system. 4. To determine the safety of favipiravir plus SOC compared to SOC alone, in this population. 5. To explore the PK of this dose regimen of favipiravir in this patient population.
Endpoints	**Primary Endpoint:** Time to viral clearance. **Secondary Endpoints:** 1. Status of Clinical recovery as measured by the study-specific 6-point ordinal scale at Day 15.

	2. Time to Clinical Recovery (TTCR) as assessed up to 29 days and defined as: a. The time (in hours) from initiation of study treatment (favipiravir + SOC or SOC alone) until normalization of fever, respiratory rate, and oxygen saturation, and alleviation of cough, sustained for at least 72 hours; or discharge. b. Normalization and alleviation criteria are defined as: i. Fever – ≤ 37.2 °C oral, ii. Respiratory rate – ≤ 24/minute on room air, iii. Oxygen saturation – SpO2 > 94% on room air, iv. Cough – mild or absent on a patient reported scale of severe, moderate, mild, absent. 3. Clinical effect as measured by the National Early Warning Score 2 (NEWS2) system. 4. All-cause mortality as assessed daily up to 29 days and at final follow up on Day 60. 5. Frequency of respiratory progression as assessed up to 29 days (daily and per SOC at each site) and defined as: a. SpO2 ≤ 94% on room air or PaO2/FiO2 < 300mmHg, and b. requirement for supplemental oxygen, or c. more advanced ventilator support. 6. Time to defervescence (in those with fever at enrollment) as assessed daily up to 29 days and at Day 60 (if possible). 7. Time to cough reported as mild or absent (in those with cough at enrollment rated severe or moderate) as assessed daily up to 29 days and on Day 60. 8. Time to dyspnea reported as mild or absent (on a scale of severe, moderate, mild absent, in those with dyspnea at enrollment rated as severe or moderate) as assessed daily up to 29 days and on Day 60 (if possible). 9. Frequency of requirement for supplemental oxygen or non-invasive ventilation as assessed daily up to 29 days and on Day 60. 10. Time to SARS-CoV-2 RT-PCR negative in upper respiratory tract specimen as assessed up to 29 days. 11. Change in SARS-CoV-2 viral load in upper respiratory tract specimen as assessed by area under viral load curve as assessed up to 29 days. 12. Frequency of requirement for mechanical ventilation as assessed up daily to 29 days and at Day 60 13. Safety of favipiravir + SOC v. SOC alone as assessed daily up to 29 days and at Day 60. 14. C-reactive protein (CRP) over time. 15. Population PK analysis of favipiravir with assessment of maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), and $AUC_{(0\text{-}24h)}$ on Days 1, 2, 8 and 14.

Study Sites	Approximately 8 sites in the U.S.A.
Planned Enrollment	Approximately 50 subjects; randomized 1:1
Study Population	Adults who are hospitalized for treatment of confirmed COVID-19
Subject Entry Criteria	**Inclusion Criteria (all questions must be answered YES)** 1. Adults (18 to 80 years old): a. within 72 hours of their hospitalization for infection with SARS-CoV-2, AND, b. within 72 hours of the latest PCR positive result and within 7 days of the 1st PCR positive result for SARS-CoV-2. (The latest PCR could be the only PCR result.), AND, c. within 10 days of onset of any COVID-19 symptoms. 2. Subject or their legal representative understands the requirements of the study and provides written informed consent prior to undergoing any treatment-related procedures. 3. If male, subject must: a. Be sterile (e.g., have had a vasectomy at least 6 months prior to Day 1 dosing), OR, b. Agree not to donate sperm during the study and for seven days following the last dose of study medication, AND, c. Agree to strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication: i. Abstain from sexual intercourse. ii. Use a condom during sexual intercourse with a female of child-bearing potential. In addition, the female partner must use another form of contraception (e.g. intrauterine device [IUD], diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants). 4. If female, subject must: a. Be unable to bear children (have not had a period for ≥ 12 consecutive months, have had her uterus or ovaries removed, or have had a tubal ligation), OR, b. Must ensure that their male partner is incapable of fathering a child (e.g., has had a vasectomy at least 6 months prior to study entry), OR, c. If she is of childbearing potential will strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication: i. Abstain from sexual intercourse, OR, ii. Must ensure that her male partner agrees to use a condom during sexual intercourse and agree to use an

	approved method of contraception (e.g., IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants). d. Agrees to stop breast-feeding prior to first dose of study drug and through seven days after completing therapy. e. Has a negative pregnancy test at screening. f. Has not had unprotected sexual intercourse within the past month. **Exclusion Criteria (all questions must be answered NO)** 1. Subject has a concomitant bacterial respiratory infection unless cleared by the Sponsor **NOTE:** Subjects on empirical antibiotic treatment for possible but unproven bacterial pneumonia, but who are positive for SARS-CoV-2, are allowed in the study. 2. Subject has a history of abnormalities of uric acid metabolism unless cleared by the Sponsor. 3. Subject has a history of hypersensitivity to an anti-viral nucleoside-analog drug targeting a viral RNA polymerase. 4. Subject is using adrenocorticosteroids (except topical or inhaled preparations or oral preparations equivalent to or less than 10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers). **NOTE:** Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of immunomodulatory medications, is permitted. Per the conclusions of The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial (https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1; accessed 13Jul2020), dexamethasone 6 mg daily (PO or IV) for 10 days is permitted. This excludes treatment with agents that have the potential for direct antiviral activity, including convalescent plasma and NO, and co-enrolment into other clinical studies that evaluate investigational agents for COVID-19. 5. Subject has a serious chronic disease (e.g., human immunodeficiency virus (HIV), cancer requiring chemotherapy within the preceding 6 months, moderate or severe hepatic insufficiency and/or unstable renal, cardiac, pulmonary, neurologic,

	vascular, or endocrinologic disease states requiring medication dose adjustments within the last 30 days). 6. Has previously received favipiravir within the past 30 days. 7. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) or glomerular filtration rate of less than 20 mL/min. 8. Has liver impairment greater than Child-Pugh A. (NOTE: Child-Pugh A subjects will have the maintenance dose decreased to 800 mg BID). 9. Has a history of alcohol or drug abuse in the previous 6 months. 10. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year. 11. Has taken another investigational drug within the past 30 days. 12. Is on another antiviral or is participating in a clinical trial for the treatment of COVID-19. 13. Subject is on ventilator at the time of study entry. 14. Is deemed by the Investigator to be ineligible for any reason.
Treatment Regimen for Favipiravir (Standard dose)	• Favipiravir tablets will be administered orally. If necessary, a slurry may be administered by nasogastric tube. • The regimen begins with loading doses of 1800 mg BID on Day 1 (the first 24 hours of treatment at t =0 and t = 12 hours) then maintenance dosing of 1000 mg BID from Day 2 (beginning 24 hours after the start of therapy). • Patients with Child-Pugh liver impairment of grade A will have their maintenance dose decreased to 800 mg BID. • The total duration of treatment is expected to be 14 days. • The dose regimen may be altered, after consultation between the treating physician and the Sponsor, depending on the clinical condition of the patient.
Duration of Study Participation	Subjects will participate in the study for up to 60 days: 14 days treatment (or as discussed with the Sponsor) and 46 days follow up.

Statistical Methods	• This study is intended to be exploratory. Based upon available data, a two-arm study of approximately 50 total subjects will be sufficient to provide reasonable assurance that the endpoints chosen for a confirmatory trial will elucidate treatment differences between favipiravir and a control. Statistical significance testing will be used to assess the relative strength of evidence of the primary and secondary endpoints.
	• Randomization will be stratified by:
	  • Site
	  • Severity of illness at enrollment:

	○ Critical disease: ▪ Requires supplemental oxygen delivered by non-rebreather mask or high-flow cannula, OR ▪ Use of invasive or non-invasive ventilation, OR ▪ Requiring treatment in an intensive care unit, use of vasopressors, extracorporeal life support. ○ Severe disease: ▪ Evidence of pneumonia on chest x-ray or CT scan, or chest auscultation (rales, crackles), OR ▪ SpO2 ≤ 93% on room air OR PaO2/FiO2 < 300 mmHg, OR ▪ Requires supplemental oxygen by nasal canula, simple face mask, or other similar oxygen delivery device. ○ Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen • There is no planned interim analysis.
Individual Stopping Rule	A subject should be removed from favipiravir treatment if one of the following criteria is met: • AST or ALT > 8 × ULN • ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN • AST or ALT > 3 × ULN AND patient has right upper quadrant pain or eosinophilia • Uric acid > 20 mg/dL
Study Measurements: Efficacy, Safety and PK	**Primary Efficacy Measurement:** Presence of virus in the nasopharyngeal and oropharyngeal samples taken on Days 1, 3, 8, 11, 15 and 29 (if hospitalized and when able to return to clinic after discharge). Swabs will also be obtained on day of discharge from hospital if discharge occurs before Day 15. **Secondary Measurements (Efficacy, Safety and PK)**: 1. 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 at Day 15 a. Not hospitalized b. Hospitalized, not requiring supplemental oxygen c. Hospitalized, requiring supplemental oxygen d. Hospitalized, on non-invasive ventilation or high flow oxygen devices e. Hospitalized, on invasive mechanical ventilation or ECMO f. Death 2. Status on the 6-point ordinal scale assessed daily while hospitalized and at each outpatient visit until Day 60. 3. NEWS2 assessed daily while hospitalized and at each outpatient visit until Day 60.

	4. Patient status assessed daily while hospitalized and at each outpatient visit until Day 60 via Study-specific Symptom Status and the ECOG Performance Status questionnaires (see Appendix A). 5. Duration of supplemental oxygen (if applicable). 6. Duration of mechanical ventilation (if applicable). 7. Duration of hospitalization. 8. Date and cause of death (if applicable). 9. Safety as assessed by: a. Observed and reported adverse events. b. Hematology and chemistry laboratories on Days 1; 3, 8, 11, 15 and 29 (if hospitalized and when able to return to clinic after discharge) c. Physical Examination at screening, Day 15 and Day 29. d. Vital signs daily while hospitalized and at each outpatient visit until Day 60 10. Qualitative and quantitative PCR and TCID50 in nasopharyngeal and oropharyngeal swabs on Days 1 (pre-dose); 3, 8, 11, 15 and 29 (if hospitalized and when able to return to clinic after discharge). Swabs will also be obtained on day of discharge from hospital if discharge occurs before Day 15. 11. Blood for determination of antibodies to SARS-CoV-2 will be obtained on Days 1, 15 and 29 (if hospitalized and when able to return to clinic after discharge). 12. Blood 6.0 ml for PK in patients randomized to favipiravir is obtained pre-dose (within 30 minutes prior to dosing) and post-dose (45 to 75 minutes following dosing) on Day 1 and trough levels on Days 2, 8 and the last day of favipiravir treatment (Day 14 unless subject leaves the study before completing treatment) and peak levels on Days 3 and 11 post-dosing. To gather these measurements – subjects will undergo 9 planned venipunctures

2 INTRODUCTION

2.1 Background Information

Favipiravir, a small molecule, is a novel anti-viral 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 and COVID-19. As of the date of this protocol, three Chinese studies exploring its use against COVID-19 have been posted to the Chinese Clinical Trial Registry website (http://www.chictr.org.cn/showprojen.aspx?proj=49042 http://www.chictr.org.cn/showprojen.aspx?proj=49015 http://www.chictr.org.cn/showprojen.aspx?proj=49013).

Results from one study have been reported as demonstrating that viral PCR titers fall faster in patients treated with favipiravir plus interferon as compared with patients treated with interferon plus lopinavir/ritonavir.

Host cellular enzymes convert favipiravir to T-705 ribosyl triphosphate (T-705RTP), which selectively inhibits viral RNA polymerase. Based on its potent and selective inhibitory activities against a broad spectrum of influenza A, B, and C viruses, including strains poorly susceptible to amantadine hydrochloride or oseltamivir phosphate, favipiravir has been approved in Japan for the treatment of uncomplicated influenza, when currently available anti-influenza medications are not sufficient.

Favipiravir has been tested against the novel corona virus COVID-19, which 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 treatment for COVID-19.

2.2 Preclinical and In Vitro Experiences

Preclinical and animal studies indicate that favipiravir is effective against RNA viruses causing a variety of disorders.

Preclinical and animal studies show no direct suppression of white blood cell types or immunosuppression by favipiravir. This contrasts with strong immunosuppressive effects of ribavirin and other antiviral agents.

Genotoxicity studies indicate that favipiravir does not pose a clinical genotoxic risk, however, based on the results of embryo-fetal toxicity studies, favipiravir is not recommended for use in pregnant females, those who may become pregnant, or those who are nursing. A human testicular toxicity study was run to determine if there are effects on human spermatogenesis. No abnormality in testicular function tests was observed; however, this study was performed at doses less than those to be used in this study. Due to the effect on embryo-fetal development seen in animals, and the presence of favipiravir in semen for several days after the end of therapy, the recommendation is for male and female contraception for seven days following the end of treatment, in the dose regimen for influenza. Details of the reproductive toxicity studies may be found in the Investigator's Brochure.

Favipiravir is both metabolized by, and inhibits, aldehyde oxidase (AO). A potential interaction exists between favipiravir and drugs oxidatively metabolized by the AO pathway, where blood concentration of these drugs or favipiravir may be increased. Similarly, a potential interaction exists between favipiravir and drugs inhibiting AO activity, where blood concentration of favipiravir may be increased. Similarly, a potential interaction exists between favipiravir and drugs inhibiting AO activity, where blood concentration of favipiravir may be increased. Favipiravir should not be used with pyrazinamide.

2.3 Clinical Experience

Overall, more than 40 clinical studies with favipiravir have been conducted globally, mainly in the US and Japan. Recently, China has begun studying favipiravir in patients with severe influenza as well as COVID-19. More than 3100 study subjects have received at least one dose of favipiravir manufactured by Toyama Chemical. Favipiravir has been well tolerated in studies

in adults and elderly subjects with uncomplicated influenza. A consistent safety profile composed of relatively low frequencies of mild to moderate adverse events (AEs) clustering around the system organ classes of gastrointestinal disorders, investigations, and infections and infestations has been characterized. Mild to moderate transient, asymptomatic elevations in serum uric acid and mild to moderate diarrhea are the two most common AEs known to occur with favipiravir. In double blind studies, the adverse event profile of favipiravir and placebo were similar with the exception of elevations of uric acid. Details can be found in the Investigator's Brochure.

Favipiravir has been used in an open label study in patients with Ebola, (2400 mg twice eight hours apart, followed by 1200 mg 8 hours later and then 1200 mg BID for the following 9-13 days). Although conclusions about efficacy cannot be reached because of the lack of a concurrent control group, favipiravir at this regimen appeared to be well tolerated. A study in Japan in patients with Severe Fever with Thrombocytopenia administered 1800 mg BID Day 1 followed by 800 mg BID for the next 13 days. It has also been used under compassionate use in patients with rabies or other unusual RNA virus illnesses.

2.4 In Vitro Therapeutic Levels

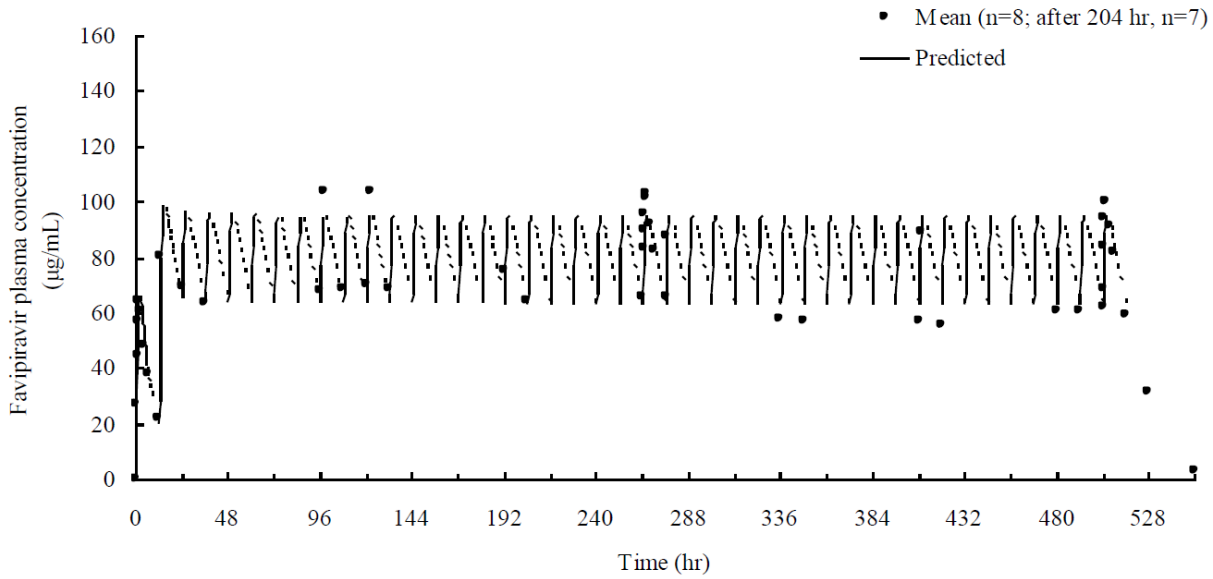
Recent in vitro experiments indicate that therapeutic levels for SARS-CoV-2 should be achievable, as illustrated in the following table:

Virus	USAMRIID	Literature
	IC_{50} (μg/ml)	
SARS-CoV-2		9.7[1] (EC_{50})
Influenza		< 4[2]
SFTS		< 4[3]
Lassa (Josiah)	10	4.64[4]
Marburg	9.9	
MERS-CoV	35.2	
Ebola	66	47[5] and 10.5[6]

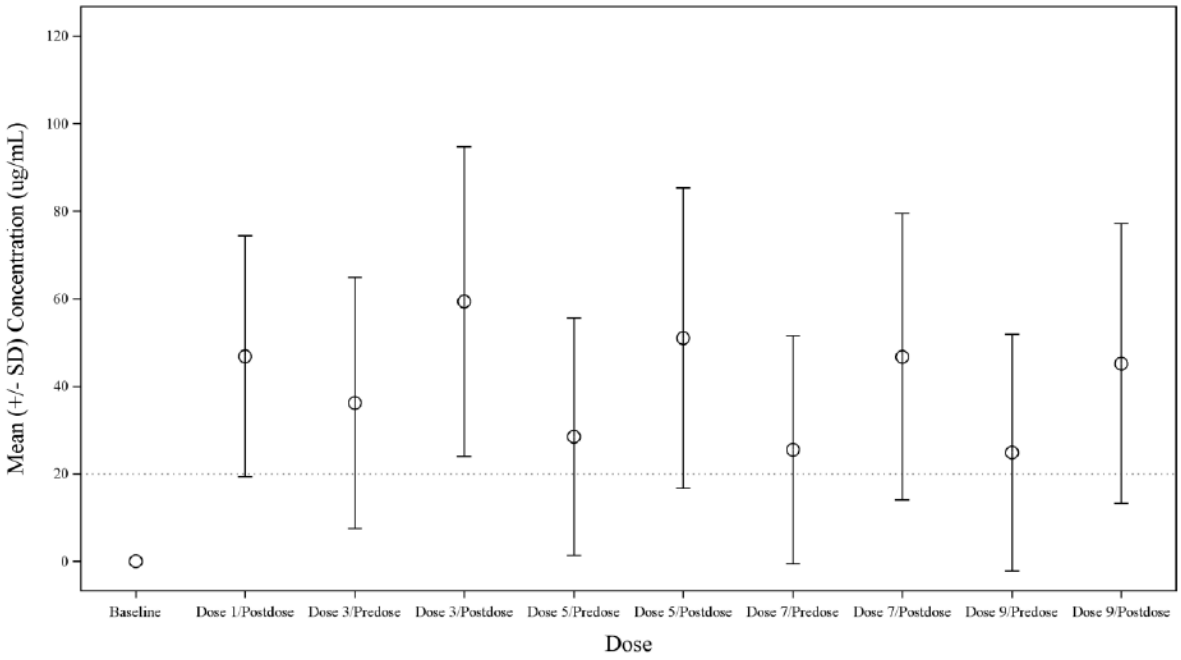
1. Wang, et al, *Cell Research* 2020 p1-3
2. Sleeman, et al, *Antimicrob Agents Chemo* 2010 **54** p2517
3. Baba, et al, *Antivir Chem Chemother* 2017 **25** p83
4. Oestereich, et al, *J Infect Dis* 2016 **213** p934
5. Smithers, et al, *Antivir Res* 2014 **104** p153
6. Oestereich, et al, *Antivir Res* 2014 **105** p17

2.5 Phase 1 Study Steady State Exposure

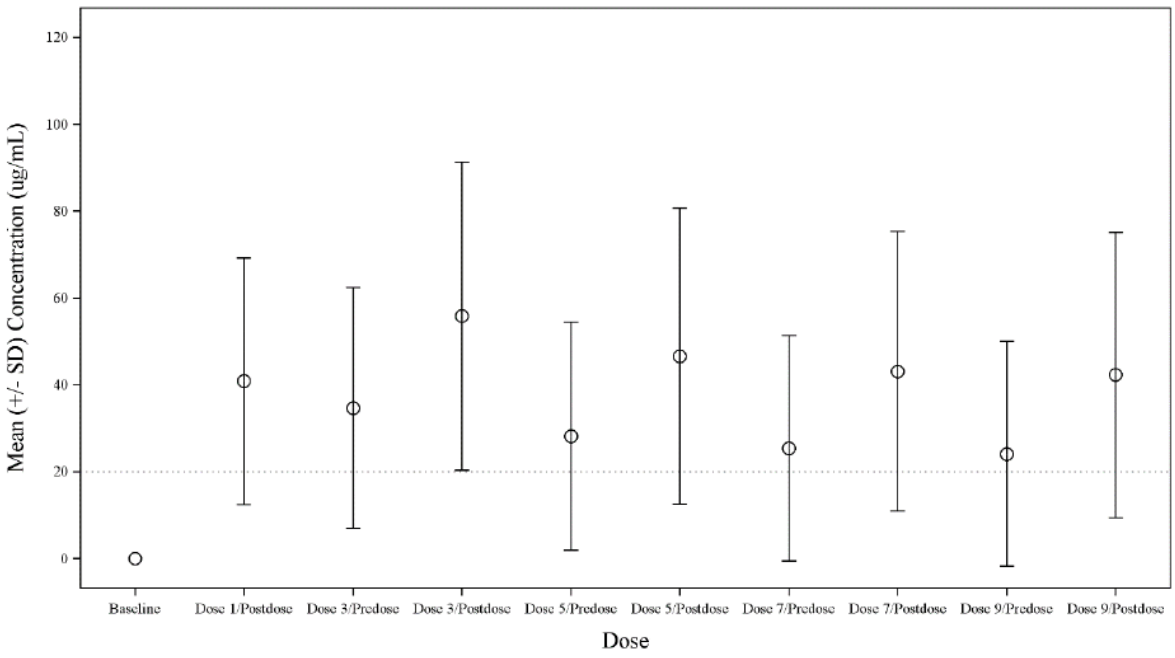
In a Phase 1 study in Japan, steady state exposures above the influenza target were achieved, which should cover the necessary exposure for SARS-CoV-2.



Similar to the PK profile above, the studies in the global influenza program using 5-days of treatment, demonstrated a similar PK profile, albeit with lower exposures. Below is the graph from US316, one of the US pivotal trials, a five-day study of 1800 mg BID Day 1 followed by 800 mg BID Days 5. As can be seen, the mean daily trough levels were above the target level of 20 ug/ml.



Below is the same graph for US317, the second pivotal trial in the program.



2.6 Rationale for 14-day Dosing Regimen

A Chinese study reported that patients in the control group (Ketruda plus aerosolized interferon) shed virus for a mean of 11 days, and the mean time to clearance in the group on favipiravir plus interferon was four days. Therefore, a mean time treatment duration of 14 days was chosen, in case interferon plus favipiravir was more effective than favipiravir alone, given the safety data supporting treatment of 10 days and beyond.

- (https://www.sciencedirect.com/science/article/pii/S2095809920300631)

2.7 Rationale for the Current Study

There is a global pandemic caused by the SARS-CoV-2 virus, which threatens the lives of many and the economic stability of the world. Therapeutic approaches are badly needed, and an orally available, well tolerated small molecule agent could play a critical part in preventing and ameliorating COVID-19.

Evidence from non-clinical (cell culture) experiments and recently reported clinical experience in China, indicates that favipiravir may have clinical benefit in patients infected with SARS-CoV-2. Favipiravir has been shown to be active against all families of RNA viruses in which it has been tested. Clear antiviral activity (faster cessation of viral shedding) has been demonstrated in the influenza studies. Patients with influenza have recovered more quickly than placebo controls.

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 co-infections and organ failure if needed. The safety profile of favipiravir is well-established. It is generally safe and well-tolerated with the exception of transient elevations of

uric acid that resolve with cessation of dosing. Thus, 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 patients with COVID-19 treated with favipiravir as compared to control. Data from this trial is expected to support a larger study which will demonstrate clinical benefit and serve as a pivotal trial for approval. The information gathered from this study will also help define the safety profile in this setting and enable expansion into other patient populations such as those who have been exposed but who are not yet ill. This could have a significant impact on public health.

3 DESIGN

This is an open label, randomized, 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 their disease to receive either favipiravir + standard of care (SOC) or SOC alone (See Section 9.5 for details).

SOC will be site-specific and based on what each site is currently using for COVID-19 patients.

The dose regimen will be 1800 mg favipiravir 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.

The study will have 14 days of treatment and 46 days of follow-up.

4 OBJECTIVES

4.1 Primary Objective

- To determine the effect of favipiravir + SOC v. SOC on viral clearance

4.2 Secondary Objectives

1. 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 WHO Master Protocol (V2.0 24FEB20) COVID-19 7-point ordinal scale] in adult patients hospitalized with COVID-19.
2. 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.
3. To explore the clinical effect of favipiravir + SOC v. SOC as measured by the NEWS2 system.
4. To determine the safety of favipiravir plus SOC compared to SOC alone, in this population.
5. To explore the PK of this dose regimen of favipiravir in this patient population.

5 SUBJECT POPULATION

5.1 Inclusion Criteria

All criteria must be confirmed as "YES":

1. Adults (18 to 80 years old):
   a. within 72 hours of their hospitalization for infection with SARS-CoV-2, AND,
   b. within 72 hours of the latest PCR positive result and within 7 days of the 1st PCR positive result for SARS-CoV-2. (The latest PCR could be the only PCR result.), AND,
   c. within 10 days of onset of any COVID-19 symptoms.
2. Subject or their legal representative understands the requirements of the study and provides written informed consent prior to undergoing any treatment-related procedures.
3. If male, subject must:
   a. Be sterile (e.g., have had a vasectomy at least 6 months prior to Day 1 dosing), OR,
   b. Agree not to donate sperm during the study and for seven days following the last dose of study medication, AND,
   c. Agree to strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication:
      i. Abstain from sexual intercourse.
      ii. Use a condom during sexual intercourse with a female of child-bearing potential. In addition, the female partner must use another form of contraception (e.g. intrauterine device [IUD], diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants).
4. If female, subject must:
   a. Be unable to bear children (have not had a period for ≥ 12 consecutive months, have had her uterus or ovaries removed, or have had a tubal ligation), OR,
   b. Must ensure that their male partner is incapable of fathering a child (e.g., has had a vasectomy at least 6 months prior to study entry), OR,
   c. If she is of childbearing potential will strictly adhere to the following contraceptive measures during the study and for seven days following the last dose of study medication:
      i. Abstain from sexual intercourse, OR,
      ii. Must ensure that her male partner agrees to use a condom during sexual intercourse and agree to use an approved method of contraception (e.g., IUD, diaphragm with spermicide, oral contraceptives, injectable progesterone, or subdermal implants).
   d. Agrees to stop breast-feeding prior to first dose of study drug and through seven days after completing therapy.
   e. Has a negative pregnancy test at screening.
   f. Has not had unprotected sexual intercourse within the past month.

5.2 Exclusion Criteria

All criteria must be confirmed as "NO":

1. Subject has a concomitant bacterial respiratory infection unless cleared by the Sponsor.

NOTE: Subjects on empirical antibiotic treatment for possible but unproven bacterial pneumonia, but who are positive for SARS-CoV-2, are allowed in the study.

2. Subject has a history of abnormalities of uric acid metabolism unless cleared by the Sponsor.
3. Subject has a history of hypersensitivity to an anti-viral nucleoside-analog drug targeting a viral RNA polymerase
4. Subject is using adrenocorticosteroids (except topical or inhaled preparations or oral preparations equivalent to or less than 10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers).

   NOTE: Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of immunomodulatory medications, is permitted. Per the conclusions of The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial (https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1; accessed 13Jul2020), dexamethasone 6 mg daily (PO or IV) for 10 days is permitted. This excludes treatment with agents that have the potential for direct antiviral activity, including convalescent plasma and NO, and co-enrolment into other clinical studies that evaluate investigational agents for COVID-19.

5. Subject has a serious chronic disease (e.g., human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, moderate or severe hepatic insufficiency and/or unstable renal, cardiac, pulmonary, neurologic, vascular, or endocrinologic disease states requiring medication dose adjustments within the last 30 days).
6. Has previously received favipiravir within the past 30 days.
7. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
8. Has liver impairment greater than Child-Pugh A. (NOTE: Child-Pugh A subjects will have the maintenance dose decreased to 800 mg BID).
9. Has a history of alcohol or drug abuse in the previous 6 months.
10. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year.
11. Has taken another investigational drug within the past 30 days.
12. Is on another antiviral or is participating in a clinical trial for the treatment of COVID-19.
13. Is on a ventilator at the time of study entry.
14. Is deemed by the Investigator to be ineligible for any reason.

5.3 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.

5.4 Individual Stopping Rule

In addition to the above, a. subject should be removed from favipiravir treatment if one of the following criteria is met:

- AST or ALT > 8 × ULN
- ALT or AST > 3 × ULN AND total bilirubin > 2 × ULN
- AST or ALT > 3 × ULN AND patient has right upper quadrant pain or eosinophilia
- Uric acid > 20mg/dL

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

6 STUDY TREATMENT - FAVIPIRAVIR

6.1 Study Drug

Favipiravir will be provided in 200 mg tablet form to be stored at controlled room temperature (15°C to 30°C [59°F to 86°F]) and shielded from light.

6.2 Standard Dose

Subjects randomized to the favipiravir + SOC arm will be administered loading doses of 1800 mg BID (Ideally 12 hours apart but 10–16 hours is allowed) on Day 1, and then maintenance dosing of 1000 mg twice daily BID (Ideally 12 hours apart but 10–16 hours is allowed) on Days 2–14 beginning 24 hours after the first dose. Day 1 is deemed to be the first 24 hours after enrollment into the study, with time 0 (time of first dose) occurring as soon as possible after the subject's eligibility has been confirmed.

An exception to the above maintenance dose will be made for those subjects entering the study with a Child-Pugh liver impairment of grade A who will receive favipiravir 800 mg BID on Days 2 through 14.

6.3 Administration of Favipiravir

Favipiravir is provided as 200 mg tablets and dosed orally. Favipiravir is rapidly and completely absorbed after oral administration of the 200 mg immediate release tablets.

If a subject cannot swallow the tablets, a slurry may be administered by nasogastric (NG) or orogastric (OG) tube. (Instructions for preparing the slurry are provided in the pharmacy instructions.). If an NG or OG tube cannot be placed, the favipiravir tablets can be crushed and administered in a "masking" substance such as apple sauce or cranberry juice.

Subjects who vomit during or immediately after dosing, should not be re-dosed.

The Investigator must consult with the Sponsor Medical Monitor prior to adjusting the dose level, regimen, or route of dosing.

6.3.1 Outpatient Favipiravir Dosing

It is possible that some subjects may improve sufficiently to be discharged from the hospital prior to Day 14. If this happens, subjects in the favipiravir + SOC arm, will be dispensed sufficient favipiravir to ensure continued dosing until their next study visit. Subjects will also be given a Diary Card to record the date and time they take their dose.

Subjects will also be instructed that if they miss a dose, they should follow the guidelines:

1) If more than 1/2 the time until their next dose has elapsed, they SHOULD NOT take the dose. They should just take the next dose at the normal scheduled time.
2) If less than 1/2 the time until their next dose has elapsed, they should take the missed dose immediately.
3) In both cases, they should then return to their regular dosing schedule.

6.4 Drug Accountability

The Investigator must maintain adequate records showing the receipt, dispensation, or other disposition of favipiravir including the date, quantity, and identification of subjects (study ID) who received favipiravir. Drug supplies will be inventoried and accounted. Unused supplies of all favipiravir will be returned to the Sponsor or destroyed on site in accordance with local procedures upon approval of the Sponsor.

6.5 Treatment Compliance

All doses of study drug will be administered by site staff while in the hospital. If the patient is discharged while still on drug, the pharmacy will provide bottles of favipiravir for outpatient use (Exact dispensing instructions for outpatients will be described in the pharmacy instructions). Assessment for compliance with each dose will be monitored and recorded in accordance with site standard operating procedures.

6.6 Treatment Precautions

An overdose is defined as any dose of study drug given to a subject or taken by a subject that exceeds the dose described in this document. In the event of an overdose, the subject should be treated symptomatically, and the Sponsor informed.

6.7 Prohibited Concomitant Therapy

The following may interact with favipiravir and risks and benefits should be carefully considered prior to treatment with the following:

- Any other anti-viral medication whether investigational or approved.
- Any drugs known to significantly inhibit AO activity (e.g., pyrazinamide, amitriptyline, chlorpromazine, clomipramine, clozapine, erythromycin, ketoconazole, nortriptyline,

quetiapine, raloxifene, perphenazine, promethazine, propafenone, tamoxifen, thioridazine).
- Any drugs metabolized by the AO pathway (e.g., famciclovir, hydralazine, lamivudine, sulindac, zaleplon, ziprasidone).
- Drugs with possible drug-drug interactions (concomitant medications requiring particular attention – see the Investigator Brochure).

For hospitalized subjects on the favipiravir + SOC arm, site staff will be reminded to consider the above prior to prescribing concomitant medications.
The following message appears on the Diary Card given to subjects that are discharged with favipiravir to take at home (see Section 6.3.1):

> *Favipiravir can slightly increase the concentration of acetaminophen (Tylenol) in the blood. Do not take more than 3000 mg (do not forget to include any acetaminophen that could be in over-the-counter preparations) in a 24-hour period as long as you are taking favipiravir.*
>
> *There are possible interactions of favipiravir with other drugs. During the time that you remain on favipiravir, do not take any medications or supplements that you were not taking while you were in the hospital, without getting approval first from the study doctor.*

Favipiravir can cause you to be mildly sensitive to sunlight. Please avoid excessive exposure to sunlight or artificial ultraviolet light (tanning machines) while you are on favipiravir.

7 STUDY PROCEDURES

Refer also to Section 13: Schedule of Assessments

7.1 Day 1 (PRE-DOSE)

- Obtain informed consent.
- Verify eligibility per the inclusion and exclusion criteria. (See Sections 5.1 and 5.2)
  - Review and record medical history, including tobacco use, to ensure there are no exclusionary illnesses.
  - Review and record concomitant medications for possible prohibited medications. (See Section 6.7)
- If subject is female of child-bearing potential and meets inclusion criteria 4.c, obtain urine or blood pregnancy test and proceed it result is negative.
- Measure and record vital signs (BP, HR, Temp, Resp).
  NOTE: vital signs to be recorded and entered in the EDC every day while subject is in the hospital and on return study visits after discharge.
- Perform Physical exam (may be done by the Principal Investigator or their designee)
- Assess and record baseline clinical status according to the following study-specific 6-point scale:
  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

NOTE: Clinical Status to be recorded and entered in the EDC every day while subject is in the hospital and on return study visits after discharge.

- Assess and record NEWS2 (See charts by clicking this link: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2
  NOTE: NEWS2 assessment to be recorded and entered in the EDC every day while subject is in the hospital and on return study visits after discharge.
- Assess and record ECOG Performance Status and Study-specific Symptom Status (see Appendix A).
  NOTE: ECOG Performance Status and Study-specific Symptom Status to be collected and recorded every day while the subject is in the hospital and on return study visits after discharge.
- Collect nasopharyngeal and oropharyngeal swabs for virologic testing. (See Virology Laboratory Manual.)
- Collect blood samples for:
  - Antibodies to SARS-CoV-2.
  - Hematology and clinical chemistry laboratory analyses
- Collect and record SpO2 by Finger Sensor
  NOTE: SpO2 to be recorded and entered in the EDC every day while subject is in the hospital and on return study visits after discharge.
- Perform subject randomization (via EDC) to establish treatment arm (favipiravir + SOC or SOC alone).
- For subjects randomized to favipiravir: Collect blood sample for PK prior to first dose (refer to PK laboratory manual for handling and shipping instructions).

7.2 Day 1 (FIRST DOSE AND POST-DOSE)

NOTE: Day 1 is deemed to be the first 24 hours after enrollment into the study, with time 0 (time of first dose) occurring as quickly as possible after the subject's eligibility has been confirmed.

- Administer first dose (1800 mg) at time 0.

Following First Dose:

- For subjects randomized to favipiravir, collect blood sample for PK within 45 to 75 minutes post-dose
- Measure and record vital signs (BP, HR, Temp, Resp).
- Collect and record SpO2 by Finger Sensor
- Administer second dose (1800 mg) at time 0 + 12 hours.
- Perform limited PE to focus on heart and lungs (may be done by the Principal Investigator or their designee).
  NOTE: to be done every day while the subject is in the hospital and on return study visits after discharge
- Collect and record adverse events (see Section 8.4 for detailed instructions)

7.3 Days 2 and 14

- Measure and record vital signs (BP, HR, Temp, Resp).
- Perform a limited PE to focus on heart and lungs.
- Review and record concomitant medications (Note: if there have been changes in concomitant medications during the study, determine whether the change is due to an AE).
- For subjects randomized to favipiravir collect blood sample for PK analysis at 30 minutes prior to any dose
- Collect and record adverse events (see Section 8.4 for detailed instructions)
- Collect and record SpO2 by Finger Sensor
- Assess and record clinical status according to the following study-specific 6-point scale:
  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
- Assess and record NEWS2
- Assess and record ECOG Performance Status and Study-specific Symptom Status (see Appendix A).
- Collect and record adverse events (see Section 8.4 for detailed instructions).

7.4 Days 3, 8 and 11

- Collect blood samples for hematology and clinical chemistry laboratory analyses
- **On Day 8** ± 1 day **only:** For subjects randomized to receive favipiravir, collect blood samples for PK trough analysis at 30 minutes prior to any dose
- **On Days 3 and 11** ± 1 day: For subjects randomized to receive favipiravir, collect blood samples for PK peak analysis at 45-75 minutes after any dose.
- Measure and record vital signs (BP, HR, Temp, Resp).
- Perform a limited PE to focus on heart and lungs.
- Review and record concomitant medications (Note: if there have been changes in concomitant medications during the study, determine whether the change is due to an AE).
- Collect and record SpO2 by Finger Sensor
- Assess and record clinical status according to the study-specific 6-point scale:
  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
- Assess and record NEWS2
- Collect nasopharyngeal and oropharyngeal swabs for virologic testing.
- Collect and record adverse events (see Section 8.4 for detailed instructions).
- Assess and record ECOG Performance Status and Study-specific Symptom Status (see Appendix A).

7.5 Days 15 and 29 (Follow-up) or Early Termination

- Perform a limited PE to focus on heart and lungs.
- Review and record concomitant medications (Note: if there have been changes in concomitant medications during the study, determine whether the change is due to an AE).
- Measure and record vital signs (BP, HR, Temp, Resp).
- Collect and record SpO2 by Finger Sensor
- Collect blood samples for:
  - Antibodies to SARS-CoV-2.
  - Hematology and clinical chemistry laboratory analyses
- Assess and record clinical status according to the following study-specific 6-point scale:
  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
- Assess and record NEWS2
- Collect nasopharyngeal and oropharyngeal swabs for virologic testing.
- Collect and record adverse events (see Section 8.4 for detailed instructions).
- Assess and record ECOG Performance Status and Study-specific Symptom Status (see Appendix A).

Note: Day 15 visit procedures may be conducted on Day 14 if patient is discharged before Day 15.

7.6 Days 45 and 60 (Additional Safety Follow-up)

Follow up assessment of general health and well-being may be done while the subject remains hospitalized or by phone if the subject has been released from the hospital and is unable to return for the study visit.

- Measure and record vital signs (BP, HR, Temp, Resp).
- Perform a limited PE to focus on heart and lungs.
- Review and record concomitant medications (Note: if there have been changes in concomitant medications during the study, determine whether the change is due to an AE).
- Collect and record SpO2 by Finger Sensor
- Assess and record clinical status according to the following study-specific 6-point scale:
  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
- Assess and record NEWS2
- Administer the ECOG Performance Status questionnaire. (See Appendix A)
- Administer the Study-specific Symptom Status questionnaire. (See Appendix A)

- Collect and record adverse events (see Section 8.4 for detailed instructions).

NOTE: if the visit is conducted by phone, vital signs, limited PE, SpO2, and NEWS2 will not be evaluated.

7.7 Day of Discharge from Hospital

- Some subjects may be well enough for discharge from the hospital prior to completing the full 14 days of treatment. In these cases, the following procedure should be followed
- FOR ALL SUBJECTS (regardless of treatment assignment)
  - The study staff will collect nasopharyngeal and oropharyngeal swabs, regardless of which study day the subject is discharged (e.g., samples should be collected on subjects discharged from the hospital on Study Day 4 even though they will have had this procedure on Study Day 3, per protocol.)
- FOR SUBJECTS TAKING FAVIPIRAVIR
  - The study staff will request the pharmacy to dispense the appropriate number of tablets for the subject to take between the time of discharge and the next scheduled study visit plus one extra day in case the visit must be changed. Prior to each study visit, the study staff will request a "refill" of favipiravir tablets to be taken by the subject between the time of the current visit and the subsequent visit. (See Pharmacy Instructions for details of dispensing.)
  - To assist the subject with compliance, dosing instructions will be provided along with the favipiravir.
  - Subjects will be reminded that the Rx bottle MAY NOT BE RETURNED TO (LEFT AT) THE SITE. To avoid contamination, each subject will bring the bottle and unused drug to their visit and show the contents of the bottle to the study staff conducting the visit. Once the drug has been counted, the subject will be instructed to dispose of the pills by placing them in a separate bag and putting the bag in the on-site trash.
  - NOTE: the site may make modifications to this procedure if needed to comply with local rules for non-contamination of the site.
  - When a subject completes dosing (either by completing all 14 days of dosing or by leaving the study) the pharmacy will send the Subject IP accountability log to the Sponsor for verification with the EDC and compliance with the protocol.

8 EFFICACY, PHARMACOKINETICS AND SAFETY ASSESSMENTS

8.1 Efficacy Assessments

Efficacy will be assessed by the following measurements:

- Presence of virus in the nasopharyngeal and oropharyngeal samples taken on Days 1, 3, 8, 11, 15 and 29 (if hospitalized and when able to return to clinic after discharge). Swabs will also be obtained on day of discharge from hospital if discharge occurs before Day 15.
- 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 at Day 15

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

- Status on the study specific 6-point ordinal scale assessed daily while hospitalized and at each outpatient visit until Day 60.
- NEWS2 assessed 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 the ECOG Performance Status questionnaires (see Appendix A).
- Duration of supplemental oxygen (if applicable).
- Duration of mechanical ventilation (if applicable).
- Duration of hospitalization.
- Date and cause of death (if applicable).
- PCR and TCID50 in nasopharyngeal and oropharyngeal swabs on Days 1, 3, 8, 11, 15 and 29 (if hospitalized and when able to return to clinic after discharge), and on day of discharge if hospital discharge occurs before Day 15.
- Blood for determination of antibodies to SARS-CoV-2 obtained on Days 1, 15 and 29 (if hospitalized and when able to return to clinic after discharge).

8.2 Required Resistance Testing

Resistance testing, as required in clinical trials of anti-viral drugs will be performed using one of the swabs, at each time point that nasopharyngeal and oropharyngeal swabs are taken.

8.3 Pharmacokinetics/Pharmacodynamics Assessments

- 6.0 mL of blood will be collected for PK sampling on:
  - Day 1 pre- and post-dosing (1st dose)
  - Days 2, 8 and 14 pre-dosing (any dose)
  - Days 3 and 11 post-dosing (any dose)
- Kits for each PK draw and instructions for handling and shipping are provided by the PK analysis laboratory.

8.4 Safety Assessments

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

Safety will be assessed by the collection of observed and reported adverse events, physical exams, vital signs, and the following clinical laboratory tests:

- **Hematology**

Hemoglobin (Hgb)	Hematocrit (Hct)
Platelet count	Red blood cell count

White blood cell count with differential

- **Chemistry**

Blood Urea Nitrogen (BUN)	Creatinine
Total bilirubin	Alkaline Phosphatase
Aspartate transaminase (AST)	Alanine transaminase (ALT)
Gamma-glutamyl transferase (GGT)	Lactic dehydrogenase (LDH)
Glucose	Albumin
Total protein	Bicarbonate
Phosphate	Sodium
Potassium	Chloride
Calcium	Total cholesterol
Urate	C-reactive protein
	D-dimer

NOTES:

- All clinical laboratory assessments listed above (hematology and chemistry) will be conducted at each site's local clinical laboratory.
- If coagulation assays are ordered as part of the SOC, the results should be added to the EDC.

Including PK and Clinical Laboratory Testing, subjects will undergo 9 planned venipunctures during this study.

8.4.1 Adverse Events

Treatment-emergent AEs will be defined as those occurring coincident with start of treatment through 46 days post-treatment (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.

Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Investigator (and/or designee) must document all AEs reported through completion of the Day 60 visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized or, if in the favipiravir arm, 14 days after last dose. The Investigator will document available follow-up information on the subject's source documentation and CRF.

8.4.2 Definition of an Adverse Event

The FDA Safety Guidance, referencing 21CFR312.32(a), defines an Adverse Event as follows:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Adverse Events are **NOT**:

- **Clinical events related to the progression of COVID-19.**
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

8.4.3 Evaluating and Reporting of Adverse Events

All AEs (i.e. a new event or an exacerbation of a pre-existing condition) that occur after dosing with favipiravir and after completion of baseline assessments in the SOC alone arm, must be recorded as an AE or SAE (if applicable), on the Adverse Event eCRF and SAE form, as applicable. The Investigator must follow all AEs until the AE resolves, or until the Investigator and/or the Medical Monitor determine the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the study, the Investigator and Medical Monitor will make a clinical assessment to determine whether continued follow-up of the AE is warranted. All subjects who have received at least one exposure to study therapy will be evaluated for safety of study treatment.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

All AEs must be promptly documented on the Adverse Event eCRF and assessed by the Investigator. Details of the event must include the dates of onset and resolution, severity, relationship to study drug, seriousness, and whether the event caused the subject to withdraw from the study, outcome and timing with regard to administration of the study drug.

Severity: Severity should be graded and recorded as follows:

- Mild: Awareness of event but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Inability to carry out usual activity, incapacitating, requires medical intervention

Relationship: The relationship of the Adverse Event to the study drug will be determined by the Principal Investigator, and assessed using the following definitions:

- **Related:** There is a distinct temporal relationship between the event onset and administration of the study drug. There is a known reaction to agent or chemical group or

predicted by known pharmacology. The event cannot be explained by subject's clinical state or other factors.

- **Unrelated:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

8.4.4 Serious Adverse Events (SAEs)

All SAEs as defined below and that occur after the first dose of favipiravir and up to Day 60 (which is 46 days after the last planned study drug administration) must be reported to the Sponsor as soon as the site becomes aware of them. Any SAEs occurring after Day 60 (more than 46 days after last planned study drug administration) and considered at least possibly drug-related must also be reported.

8.4.5 Definition of Serious Adverse Events

An SAE is an AE from this study that results in any of the following outcomes:

- Death **(even if caused by COVID-19 all deaths are recorded as SAEs)**
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug

NOTE: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject *and* may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A life-threatening AE is defined as any adverse experience that places the subject in the view of the Investigator, at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

"Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. Presentation and care within an emergency department does not necessarily constitute an SAE. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, it is an SAE.

8.4.6 SAE Reporting Requirements to the Sponsor

The procedure for reporting SAEs, regardless of causal relationship, is as follows:

- Within 24 hours of the Investigator's knowledge of an SAE, the site must notify the Sponsor by phone call to their site monitor, medical monitor or other Sponsor representative. They should also immediately complete the AE eCRF and select "Serious".
- This initial reporting of an SAE should contain as much information as is available to the Investigator. Submission of the SAE via the EDC should not be delayed in order to collect additional information to complete the form.
- Follow-up SAE reports may be generated in cases in which additional information becomes available. Hospital records, autopsy reports, and other documents may become available and scanned copies can be provided to the Sponsor when applicable. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.
- The Sponsor will distribute completed SAE forms, which may be used to notify the IRB when applicable, via a secure internet-based document depository.
- The Investigator should notify the IRB of Serious Adverse Events occurring at the site and other adverse reports received from the Sponsor in accordance with local procedures.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF.

8.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR carries specific and time-based reporting requirements for the Sponsor of a clinical trial. Thus, after an Investigator reports an SAE, the FDA expects the Sponsor will determine whether it meets the definition of a SUSAR.

A SUSAR is defined according to 3 criteria:

1. The AE is deemed a "suspected adverse reaction" if there is a reasonable possibility that the study drug caused the AE. A "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and adverse event.
2. The AE is "Serious" if it meets the definition of an SAE provided in section 8.4.5
3. The AE is deemed "unexpected" if it is not listed in the Investigator's Brochure (IB) or if in the IB, has not been reported at the severity observed.

In cases where the Sponsor deems a SUSAR has occurred, it must file an IND Safety Report with the FDA. FPHU will require the assistance and cooperation of the Investigator and staff to provide accurate and complete information on the subject and observed SAE so that reporting requirements to the FDA can be met.

8.5.1 Reporting SUSARs to the FDA: IND Safety Reports

IND safety reports are used to submit reports of SUSARs to the FDA. There are 2 types of reports:

- A "15-day report" is used when the reported SAE is a SUSAR and requires that as much information as is available to the investigator and the sponsor, be submitted to the FDA in on

the appropriate form. For US trials, the appropriate form is the FDA Form 3500A also commonly known as a "MedWatch" form.

- A "7-day report" is used when the SUSAR is considered to be fatal or life-threatening.

The 7-day and 15-day timelines begin the day that the Investigator learns of the event and are counted in calendar days – not business days. Therefore, it is important that the investigator carefully follow the reporting requirements described in section 8.4.6.

8.6 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs unless considered to be clinically significant by the site clinician. An abnormal laboratory result will be considered an AE if it induces clinical signs or symptoms, if the abnormality is of a degree that requires active management (e.g. discontinuation of the study drug, dose modification) or when the event is requiring treatment or other therapeutic intervention (e.g. iron supplements, blood transfusion, etc.).

The Investigator will evaluate the relationship of any significantly abnormal result to protocol treatment and clinical condition, if possible. All clinically significant abnormal laboratory results will be followed until they return to normal or become stabilized.

8.7 Handling of Overdose

An overdose is defined as any dose greater than the highest daily dose included in this document. Any overdose must be recorded. If the overdose is associated with an AE, that AE must be recorded, assessed for seriousness, and reported as an SAE.

9 STATISTICAL METHODS

9.1 General Considerations

This study is intended to support a Phase 3 registrational trial in this patient population by providing information on the treatment effect on an unambiguous indicator of antiviral activity, i.e., the time to viral clearance, as well as to estimate the treatment effect on a number of important clinical and symptomatic disease correlates. Proof of concept will be established by a significant treatment effect on the primary endpoint of time to viral clearance. Based upon available data, a two-arm study of approximately 50 total subjects will be sufficient to provide reasonable assurance that the endpoints chosen for a confirmatory trial will elucidate treatment differences between favipiravir + SOC and SOC. Statistical significance testing will be used to assess the relative strength of evidence of the primary and secondary endpoints; given that this trial is intended as a proof of concept, a two-sided alpha-level of 0.10 will be used for significance testing.

It is important to ensure that reasonable certainty is achieved in the conclusions reached for key secondary endpoints, therefore key secondary endpoints will be adjusted for multiple statistical testing through a gatekeeping hierarchical methodology, as follows: Statistical significance for the first secondary endpoint, according to the order outlined in the endpoints section of this protocol, will be declared only if the primary endpoint has previously reached statistical significance. Subsequent endpoint analyses in the order presented will be declared significant

only if the previous endpoint in order has reached statistical significance. All analyses of secondary endpoints will also be conducted at the two-sided alpha-level of 0.10. The order of secondary endpoint analysis will be the following: the study-specific 6-point ordinal scale; time to clinical recovery; reduction in disease symptoms; reduction in oxygen/ventilation requirements.

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, 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. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented, as well as 2-sided 95% confidence intervals (CIs). Summaries of categorical data will include counts and percentages, along with 2-sided 95% CIs. Kaplan Meier methods will be used to summarize the time-to-event endpoints, including 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of events and censored observations.

Complete details of all statistical analyses, including methods for handling missing data, will be included in a formal statistical analysis plan (SAP), to be completed as soon as possible after study initiation.

9.2 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 SOC would likely be approximately 11 days; this latter estimate may in fact 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) would be required.

9.3 Demographic and Baseline Characteristics

Summary statistics will be provided per treatment group for demographic (e.g., age, height, weight, body mass index [BMI], race, gender) and other initial subject characteristics (e.g., medical history, concomitant diseases) will be provided per treatment group and for the total group. The ITT population will be used for the summaries.

9.4 Analysis Populations

The following analysis populations will be defined for the study:

- 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 safety population that have an assessment of viral shedding after randomization and are confirmed COVID-19 positive. 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 and have an outcome assessment. Further specific details defining the analyses to be performed on this population will be described in the SAP.
- PK population (PK) – All subjects in the safety population that have at least one result that can be used in the PK summaries.

9.5 Stratification, Subgroup Analysis and Pooled Analysis

The stratification factors used in randomization, critical v. severe v. mild/moderate disease as defined above based on supplemental oxygen requirements, SpO2 status etc., will be accounted for in the efficacy analyses. The stratification factor may be deleted from the statistical model if the interaction is not significant at the 0.10 level. Efficacy data will be pooled across study sites for analysis, after visual inspection of summary results reveals similarity across study sites. Efficacy results may also be summarized within each randomization stratum for exploratory purposes.

9.6 Efficacy Endpoint Analysis

The primary endpoint of time to viral clearance will be analyzed with the log-rank test for treatment difference and summarized using the Kaplan-Meier methodology as noted above. Viral load results from day of discharge as available will also be included in the analysis of viral clearance.

The key secondary endpoint of status of clinical recovery as measured by the study-specific 6-point ordinal scale at Day 15 will be analyzed using ordinal categorical data methods, since it is unlikely that linear differences exist between the elements of the scale (for example, a 1-point difference in magnitude may not apply to each increment on the scale). As an exploratory analysis, sequential binary analysis will be performed, based on successive classification of a subject into categories of less than or greater/equal to each ordinal item on the scale. Longitudinal analysis of the 6-point scale over time on study will also be performed to investigate temporal patterns of improvement.

Time to event endpoints will be analyzed using similar methods as used for the primary endpoint; these will include time to: clinical recovery; defervescence; cough mild or absent; dyspnea mild or absent; SARS-CoV-2 RT-PCR negative in upper respiratory tract.

Categorical endpoints will be analyzed using categorical data analysis methods; continuous data will be analyzed using analysis of variance with treatment and strata as factors.

Missing efficacy data in a trial of hospitalized patients is generally unlikely, and great care will be taken at each study site to ensure that all outcome assessments are obtained as planned in this protocol. However, as treatment of COVID-19 subjects evolves, it is clear some subjects will be discharged from the hospital prior to Day 15. Subjects are asked to return for follow up visits on Days 29, 45 and 60. This requirement is presenting challenges for subjects and in order to ensure that in cases where the subject does not return for their follow up visits, an additional swabbing has been added on the day of hospital discharge (See Section 7.7). Should missing data occur for the primary endpoint, time to viral clearance, such patients will be included in the log-rank analysis as censored observations. Missing clinical outcome data will be evaluated using a variety of methods, including multiple imputation, worst-value assignment, and other methods, to be completely outlined in the statistical analysis plan.

9.7 Safety Analysis

The original exact terms in the electronic data capture (EDC) system used by Investigators to identify AEs other than symptoms of COVID-19 will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be defined as those occurring coincident with start of treatment and through Day 60. TEAEs will be summarized overall and by treatment group and by MedDRA body organ system and preferred term, severity, relatedness, and seriousness.

An overall summary of TEAEs will be presented by treatment, with subject counts and percentages of subjects with the event. This summary will include subjects with any TEAE, any treatment-related TEAE, any serious TEAE, any treatment-related serious TEAE, TEAEs leading to study infusion discontinuation, treatment-related TEAEs leading to study infusion discontinuation, TEAEs leading to death, and treatment-related TEAEs leading to death. The difference in proportions between treatment groups in each of these categories will be calculated.

Summaries of changes over time in laboratory parameters, as well as counts and percentages of laboratory parameters that are Low, Normal, and High compared to the reference ranges will be presented by treatment at each visit and time point. Shift tables will be presented for laboratory parameters with defined severity grades.

10 RECORDING AND COLLECTION OF DATA

10.1 Case Report Form

The Investigator or designee will record all data collected on the electronic Case Report Form (eCRF) provided for that purpose. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures.

All site entries will be made in a secured web site and the Principal Investigator will review the record for completeness. Upon completion of the review, the PI will sign electronically in the signature page of the eCRF.

The Investigator or designee will make necessary eCRF corrections. The investigator must authorize the corrections to the entered data on eCRF.

Specific instructions on use of the EDC system and guidelines for data entry and correction will be provided to the sites.

10.2 Study Files and Subject Source Documents

Subject confidentiality is strictly held in trust by the participating investigators, research staff, the Sponsor and their designees. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a subject identification number to maintain confidentiality.

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigators' Study Files and original subject clinical source documents generated at the study site. The term "original" means the first recording of the data.

The Investigator will ensure the site master files are maintained, including the study protocol and its amendments, IRB and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Subject clinical source documents may include, but are not limited to, subject hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, and consultant letters. The Investigator must assure that all original source documents are available to support monitoring activities.

10.3 Monitoring

Due to the restrictions imposed on clinical and hospital visits by the COVID-19 pandemic, all monitoring of this study will be conducted remotely. Monitors will work with the Study Coordinator at each site to determine times for "joint" remote monitoring – meaning that the monitor and the SC will review data together over the telephone.

Remote monitoring will be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Investigator will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of remote monitoring and by prompt attention to any matters brought to his/her attention by the monitor.

10.4 Audit

ICH guidelines for GCP require independent inspection of clinical program activities. Such inspections may be performed at any time - before, during and/or after the study. The Investigator and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by the Sponsor that will be suitable for inspection at any time by the Sponsor, its designees, and/or regulatory agencies. The Investigator understands and agrees to give access to the necessary documentation and files.

10.5 Retention of Data

All records connected with this clinical study will be retained for at least two years following the date of an approved marketing application [21 CFR 312.62(c)]; or at least three years from the formal discontinuation of favipiravir development; or seven years from the end of the study, whichever is longer. All local laws regarding retention of records must also be followed. Study sites are required to retain all records until written notification allowing destruction is received from the Sponsor.

11 ETHICS

11.1 Ethics Committee

A properly constituted, valid IRB/IEC must review the treatment plan and procedures, the Investigator's informed consent document, and related subject information. It is the responsibility of the Investigator to ensure that all aspects of institutional review are conducted in accordance with current regulations governing the jurisdiction where the study is conducted. The Sponsor (or designee) must receive a letter documenting IRB/IEC approval that specifically identifies the title of the treatment plan, subject information sheet, and ICF.

11.2 Subject Information and Consent

It is the responsibility of the Investigator to ensure that written informed consent is obtained from the subject or legal representative before any activity or procedure is undertaken that is not part of routine care. The informed consent must comply with local regulations.

The background of the study, the procedures, the potential benefits and risks of the treatment, and the fact that treatment is voluntary for the subject must be explained to the subject or legal representative. The subject or representative must be given sufficient time to consider whether to consider whether or not to participate in the study. A copy of the ICF, signed and dated by the subject/representative and the Investigator (or designee), must be given to the subject/representative. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any treatment with favipiravir.

Each consent form should contain an authorization allowing the Investigator and the Sponsor (or designee) to use and disclose protected health information (PHI) (i.e., subject-identifiable health information) in compliance with local law. The signed consent form will be retained with the treatment records.

12 GENERAL CONSIDERATIONS

12.1 Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at any time for any reason.

12.2 Use of Information and Publication

All information concerning favipiravir, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, formulation, and other information supplied by the Sponsor to the Investigator and not previously published is considered confidential and

remains the sole property of the Sponsor. The Investigator agrees to use this information only to treat this patient and will not use it for other purposes without written consent of the Sponsor.

The information obtained in this study will be used by the Sponsor in connection with the continued development and, if approved, commercialization of favipiravir. Thus, Sponsor may disclose such information as required to other clinical Investigators, contractors, and government regulatory agencies.

Publication or other public presentation of results from this study and related information is subject to the provisions of the Clinical Trial Agreement between Sponsor and the Study Site.

13 SCHEDULE OF ASSESSMENTS

ASSESSMENT	HOSPITALIZED							FOLLOW UP Outpatient 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	DAYS 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]			
SpO2 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 and $TCID_{50}$	X			X[11]	X[11]	X[11]		X	X	
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

	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**	**DAYS 45 and 60 ± 2 days[8]**
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 (1800 mg BID on Day 1000 mg 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 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. SpO2
   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 to 75 minutes post-dose
7. Maintenance dose for CP score A is 800 mg BID.
8. Days 45 and 60 may be completed in the hospital, outpatient 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 $TCID_{50}$ 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.

Appendix A: Subject Status Scales

1. ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

2. Study Specific Symptom Status Scale

Symptom	Present? Y/N	Severity: Mild, Moderate, Severe
Feeling Feverish		
Dyspnea		
Cough		
Use of Antibiotic		