A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects with Mild or Asymptomatic COVID-19

Study Protocol and Statistical Analysis Plan

NCT04346628

February 18, 2021

A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects with Mild or Asymptomatic COVID-19

PROTOCOL NUMBER: IND [redacted]

IND#: [redacted]

INVESTIGATIONAL PRODUCT: Favipiravir **(T-705)**

PROTOCOL VERSION / DATE: Version 9: 18Feb2021

Amendment Version 8: 12Feb2021
Amendment Version 7: 30Oct2020
Amendment Version 6: 07Oct2020
Amendment Version 5: 29Sep2020
Amendment Version 4: 04Aug2020
Amendment Version 3: 29Jul2020
Amendment Version 2: 17Jul2020
Original Version 1: 30Jun2020

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PROTOCOL SIGNATURE PAGE

Protocol Title: A Phase 2 Randomized, **Double Blinded, Placebo Controlled Study** of Oral Favipiravir Compared to Standard Supportive Care in Subjects with Mild or Asymptomatic COVID-19

Protocol Number: PIND [redacted]

Protocol Version/Date: Version 8 / 18Feb2021

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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)

Statement of Compliance

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Site Investigator Name: _____

Site Investigator Signature: _____

Date: _____
Date (MM/DD/YYYY)

TABLE OF CONTENTS

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	A Phase 2 Randomized, **Double Blinded, Placebo Controlled Study** of Oral Favipiravir Compared to Current Standard of Care in Subjects with Mild or Asymptomatic COVID-19
Design	This is a Phase 2 **Double Blinded, Placebo Controlled Study** evaluating the efficacy, safety and pharmacokinetics of favipiravir in adult subjects with PCR-positive, mild or asymptomatic COVID-19 infections. The study is a multicenter trial that will be conducted in up to 5 sites nationwide. Subjects will be randomized to receive either favipiravir + current Standard of Care (SOC) or placebo + SOC. For those subjects in the favipiravir + SOC arm, the dose regimen will be 1800 mg BID favipiravir on the first dose (day 1) followed by 800 mg BID for the next 9 days (days 2-10). NOTE: 600 mg BID for subjects with Child-Pugh A liver impairment on days 2-10. Subjects in the SOC arm will receive placebo. The total anticipated duration of the study for each patient is 28 days.
Objectives	**Primary Objective** To evaluate the efficacy of oral favipiravir plus SOC compared with placebo plus SOC in reducing the duration of shedding of SARS-CoV2 virus in patients with mild or asymptomatic COVID-19. **Secondary Objectives** 1. To evaluate the efficacy of oral favipiravir compared with placebo in reducing the onset or duration of symptoms, hospitalizations, or ED visits in patients with mild or asymptomatic COVID-19. 2. To assess the safety and tolerability of favipiravir in this subject population. 3. To assess the development of antibodies against SARS-CoV-2 4. To evaluate any changes in the PK profile of favipiravir and its major metabolite M1 in this subject population
Endpoints	**Primary Endpoint:** Time until cessation of shedding of SARS-CoV-2 virus, defined as the time in days from randomization to the first of two consecutive negative RT-PCR results of self-collected nasal swabs. **Secondary Endpoints** 1. Nucleic acid (RT-PCR) from oropharyngeal swabs collected on Days 1, 5, 10, and 28

	2. Clinical worsening of COVID-19 in symptomatic subjects (clinical worsening defined the development of respiratory distress or symptoms that require hospitalization) or development of COVID-19 symptoms in asymptomatic subjects 3. Adverse events AEs and clinical laboratory tests for systemic safety including hematology and clinical chemistry 4. Development of antibodies to SARS-CoV-2 5. Time until cessation of symptoms (cessation of symptoms defined as absence of symptoms for at least 24 hours for those with mild symptoms). 6. Absence of development of any symptoms among those enrolled with asymptomatic infection. 7. Population PK analysis of favipiravir with assessment of maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) on Days 1, 5 and 10
Study Sites	Stanford University School of Medicine
Planned Enrollment	180 (90 in the favipiravir + SOC group and 90 in the placebo + SOC group)
Study Population	Adults with confirmed SARS-CoV-2 who are asymptomatic or experiencing mild to moderate symptoms
Subject Entry Criteria	**Inclusion Criteria (all questions must be answered YES)** 1. Adults (18-80) 2. Diagnosis of COVID-19 disease: a. If symptomatic, but without signs of respiratory distress (as defined by SpO2 <=94% on room air, RR >=24, HR >=110), with FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from initial swab to the time of commencing informed consent: Mild disease is defined as having at least 1 of the following: i. Fever (>98.7F) b. Cough/Shortness of breath/dyspnea c. Fatigue d. Headache/Body aches e. Joint pain f. Chest pressure g. GI symptoms including nausea, vomiting, and/or diarrhea h. Abdominal pain i. Sore throat j. Nasal congestion k. Chills l. Runny nose

	m. New loss of taste or smell n. Abdominal pain o. Rash The date of onset of the first of the above symptoms will be documented. p. If asymptomatic, initial diagnosis obtained no more than 72 hours from initial swab to the time of commencing informed consent 3. Subject or their legal representative understands the requirements of the study and provides written informed consent prior to undergoing any treatment-related procedures. 4. If male, subject must fulfill one of the following criteria: 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). 5. If female, subject must fulfill one of the following criteria: 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 their 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 urine pregnancy test at screening. 6. Subject agrees to maintain home or other quarantine as recommended by the study physician, except to visit the study site as required by the protocol. 7. Subject agrees to take daily nasal swabs (anterior nares) for Day 1 to Day 10 and Day 14, 21, and 28 using the study provided materials, and mail via FEDEX each sample on the day collected. 8. Subject agrees to record daily symptoms, temperature, oxygen saturation, and pulse using the study provided materials. 9. Subject agrees to return to the study site for follow-up visits on Day 5, 10, and 28. The study site will be staffed by trained healthcare providers wearing full personal protective equipment and study site equipment will be disinfected between patients according to the same protocols as a clinical setting. Subjects will be wearing masks, will be appropriately spaced, and the number of subjects assessed at each time will be limited. **10.** Members of the same household may participate in the study as long as the inclusion and exclusion criteria are met. **Exclusion Criteria (all questions must be answered NO)** 11. Subject has a concomitant bacterial respiratory infection as documented by a respiratory culture with microbiologic growth. **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. 12. Subject has a history of abnormalities of uric acid metabolism. 13. Subject has a history of hypersensitivity to an anti-viral nucleoside-analog drug targeting a viral RNA polymerase. 14. Subject has any of the following abnormal laboratory test results at screening: a. Platelet count <100,000 cells/mm^3 b. Absolute lymphocyte count <500 cells/mm^3 c. Hemoglobin <11 g/dL for women and <12 g/dL for men d. Serum creatinine concentration ≥1.5× ULN e. Confirmed creatinine clearance (CrCl) < 50 mL/min by Cockcroft-Gault f. Serum uric acid >20 mg/dL g. 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:** *Clinical screening laboratory evaluations will be performed locally by the site or site-designated laboratory.* Treatment of study participants following institutional COVID-19 treatment policies or guidelines, including the use of immunomodulatory medications, 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. 15. Subject has a serious chronic disease (e.g., human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months, and/or moderate or severe hepatic insufficiency and/or unstable renal, cardiac, pulmonary, neurologic, vascular, or endocrinologic disease states per investigator judgement). 16. Has previously received favipiravir within the past 30 days. 17. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). 18. Has liver impairment greater than Child Pugh A. 19. Has a history of alcohol or drug abuse in the previous two years. 20. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year. 21. Has taken another investigational drug within the past 30 days. 22. Is deemed by the Investigator to be ineligible for any reason.
Randomization	Following consent, those subjects meeting all entry criteria will be randomized in a 1:1 ratio. Treatment Arm: favipiravir + SOC Control Arm: placebo + SOC Randomization will be stratified by age (>=50 and <50 years old) and sex.
Treatment Regimen for Favipiravir (Standard dose)	• Favipiravir and placebo tablets will be administered orally. • The regimen begins with loading doses of 1800 mg BID on Day 1 (the first 24 hours of treatment at t =0 and t = 8-12 hours) (3600

	mg/day). Then maintenance dosing of 800 mg BID (1600 mg/day) from Day 2 (beginning 18-24 hours after the loading dose on Day 1). • Patients with Child-Pugh liver impairment of grade A will have their maintenance dose decreased to 600 mg BID • The total duration of treatment is expected to be 10 days.
Duration of Study Participation	The total anticipated duration of the study for each patient is up to 28 days.
Statistical Methods	To address our primary objective, time until viral shedding cessation will be compared between the two treatment arms using a two-sided Wald test derived from a Cox proportional hazards model adjusted for age and sex and stratified by site. The test will be performed at the two-sided alpha = 0.05 level of significance. The hazard ratio for shedding cessation will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption. The log rank test will also be performed. The distribution of viral shedding cessation will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to shedding cessation along with 95% confidence intervals will be presented for each treatment arm. The rate of hospitalizations and ED visits will be estimated along with 95% confidence intervals by each arm. In addition, we will compare between arms the time to each of respiratory failure, hospitalization or deaths and the corresponding composite of all such events using Kaplan-Meier methods. The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set. An interim analysis for safety and overwhelming efficacy will be performed once 50% of patients have 24 hours of follow-up complete. Enrollment will pause once 50% of patients have received treatment and will remain paused until the DSMC makes their recommendation after their safety review.
Individual Stopping Rule	A subject should be removed from favipiravir treatment if one of the following criteria is met: • AST or ALT > 8 x ULN • ALT or AST > 3 x ULN AND total bilirubin > 2X ULN • AST or ALT > 3 x 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.
Study Measurements: Efficacy, Safety and PK	**Primary Measurement (Efficacy):** 1. Time to first of two negative tests based on nasal swab for RT-PCR taken daily from Day 1 to Day 10, and Days 14, 21, and 28. **Secondary Measurements (Safety, Efficacy and PK)**: 2. Oropharyngeal swab for nucleic acid (RT-PCR) taken Day 1, 5, 10, and 28. 3. Symptom improvement or worsening: Subjects will fill in a diary daily, recording the following symptoms: a. Cough b. Sore throat c. Headache d. Nasal congestion e. Body aches and pains f. Fatigue g. Oral temperature taken after 4 pm and at least four hours after ingesting the most recent antipyretic (acetaminophen or NSAID) h. Dyspnea i. Shaking chills j. New loss of taste or smell k. GI symptoms including nausea, vomiting, and/or diarrhea l. Chest pain 4. Safety as assessed by: a. Observed and reported adverse events b. Clinical laboratory evaluations of blood on Days 1, 5, 10, and 28 c. Physical Examination at screening (pre-dose Day 1), Days 10, and 28 d. Daily vital signs: pulse oximetry, heart rate, and temperature. 5. Optional Blood for determination of antibodies to SARS-CoV-2 will be obtained on Days 1 and 28. Collection of blood for antibodies is optional for sites. 6. Optional Blood for PK obtained pre-dose (within 30 minutes prior to dosing) and post-dose (45 to 75 minutes following dosing) on Days 1, 5 and 10. Collection of PK is optional for sites. 7. Optional Stool samples for determination of viral load in stool and microbiome characterization will be obtained in the following

	windows Day 1±5, 14±7, and 28±7. Collection of stool is optional for sites.

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 coronavirus SARS-CoV2, which causes disease ranging from mild, cold-like symptoms to acute respiratory failure and death. Epidemiologic studies suggest that individuals can be asymptomatic and transmit disease. The only available treatment for COVID-19 illness is remdesivir but it's use is currently limited to hospitalized patients with severe disease under an emergency use authorization from the FDA.

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]

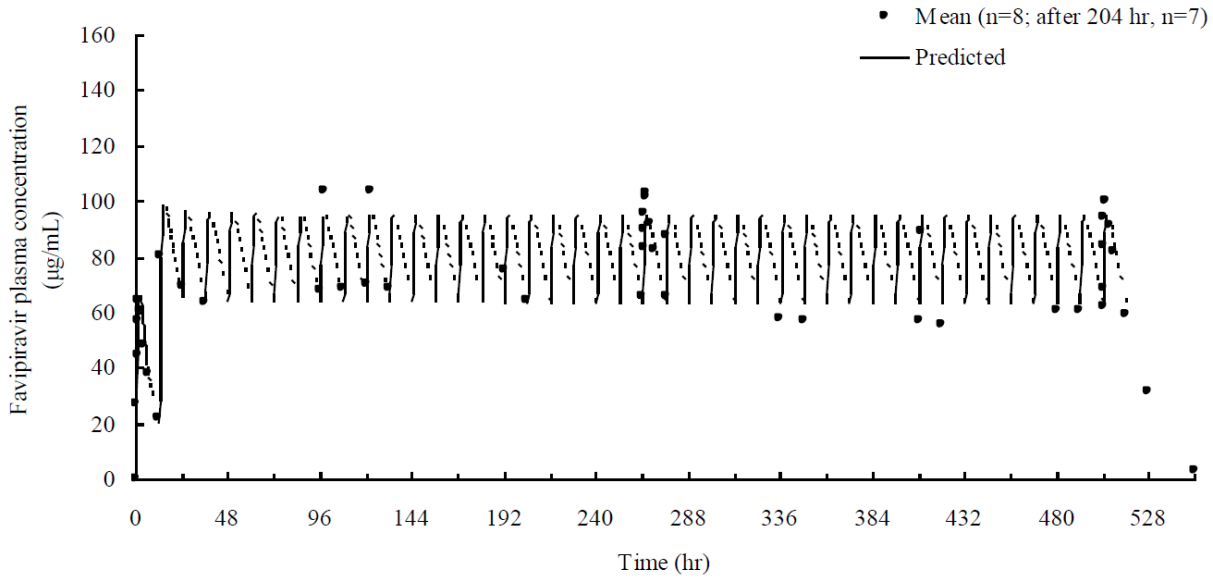
1. Wang, et al, *Cell Research* 2020 p1-3

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

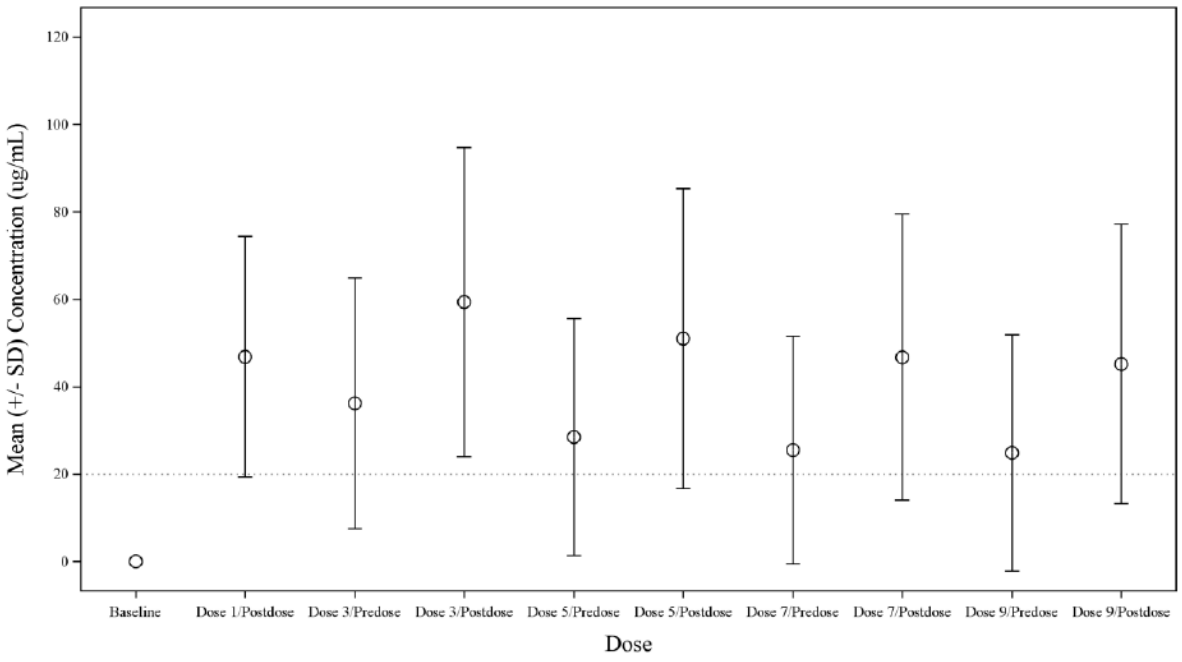
Unpublished data from different labs report EC50s of 32 and >15.7 ug/mL for SARS-CoV-2. Several other labs have reported that the same cell lines and viral strains of influenza can result in up to four-fold differences in susceptibility on different days (data on file). The optimal cell lines for studying SARS-CoV-2 has not been determined, and no animal models have been developed as yet. Additional experiments are being planned.

2.5 Phase 1 Study Steady State Exposure

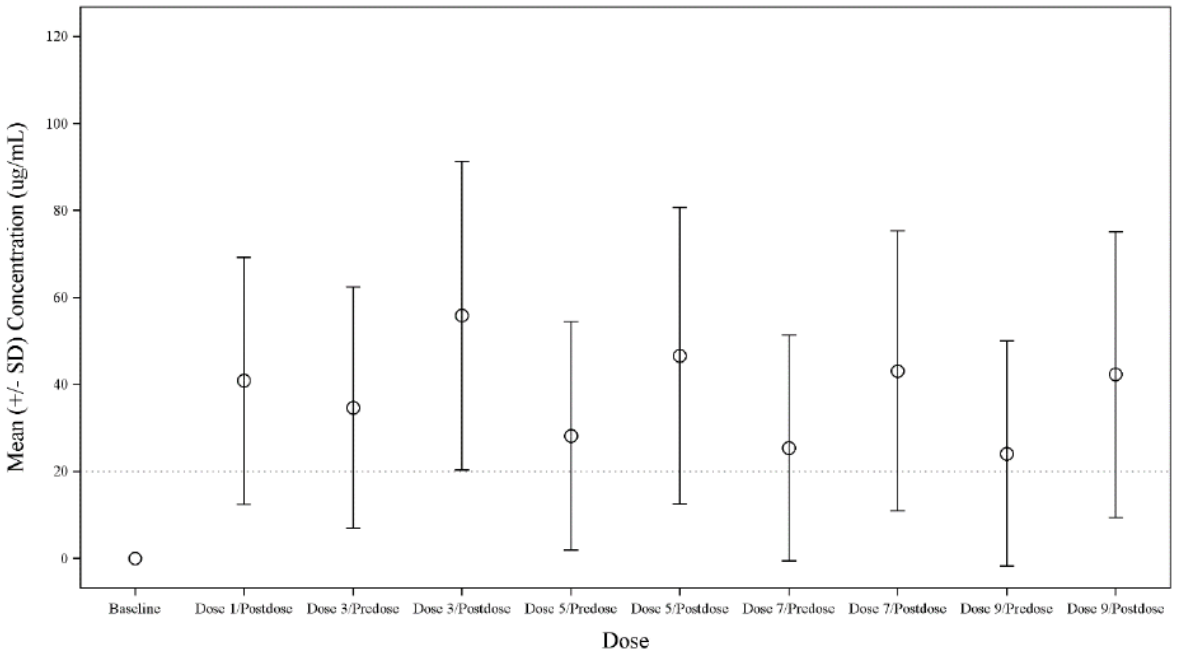
In a Phase 1 study in Japan, steady state exposures above the influenza target were achieved, which should cover the necessary exposure for SARS-CoV-2.



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 10-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 influenza studies. Patients with influenza treated with favipiravir have recovered more quickly than placebo controls.

People with COVID-19 who are asymptomatic or experiencing mild to moderate symptoms that do not require hospitalization have no proven option other than supportive care. 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. Furthermore, reducing viral shedding may decrease household and community transmission of SARS-CoV2. 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

3.1 Study Design

This is a Phase 2 Double Blinded and Placebo Controlled Study evaluating the safety, pharmacokinetics, and efficacy of favipiravir in adult subjects with PCR-positive, asymptomatic, or mild COVID-19 infections.

Subjects will be randomized to receive either favipiravir + current local Standard of Care (SOC) or placebo + SOC. SOC at Stanford is defined as methods Stanford University Healthcare is using for COVID-19 patients at the time of study initiation. Each site's local SOC to be defined and shared with Sponsor prior to study initiation.

For those subjects in the favipiravir + SOC arm, the dose regimen will be 1800 mg BID favipiravir on the first dose (day 1) followed by 800 mg BID for the next 9 days (days 2-10). NOTE: 600 mg BID for subjects with Child-Pugh A liver impairment on days 2-10.

Subjects in the SOC arm will receive placebo. The total anticipated duration of the study for each patient is 28 days.

3.2 Study Sites

This study is being supported by the Stanford Innovative Medicines Accelerator (IMA), Clinical Trials Research Unit (CTRU), and the Stanford Center for Clinical Research. This study may be performed at up to 5 sites nationally.

Each investigator or group of investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit all required regulatory documents (including any protocol specific documents) to their respective IRB as required per institution. Sites can submit through a Stanford-designated central IRB for this trial. All subsequent mentions of IRB related activity in this document will reflect whichever choice they decide, be it local or central IRB.

Requirements for site selection and site registration: Sites will be evaluated by Stanford team and the main PI prior to selection or activation.

Stanford requires documentation that verifies IRB-approval for this protocol, informed consent documents, and associated documents prior to recruitment, screening, and enrollment of subjects, and any IRB-approvals for continuing review or amendments.

Please refer to the MOP for information on:

- Requesting and submitting regulatory documents
- Patient enrollment & randomization
- Randomization notification
- Requesting study drug
- Withdrawals
- Lost to follow-up
- Protocol deviations
- Data submissions

4 OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of oral favipiravir plus SOC compared with placebo plus SOC in reducing the duration of shedding of SARS-CoV2 virus in patients with mild or asymptomatic COVID-19 disease.

4.2 Secondary Objectives

1. To evaluate the efficacy of oral favipiravir plus SOC compared with placebo plus SOC in reducing the duration of symptoms, hospitalizations, or ED visits in patients with mild or asymptomatic COVID-19 disease.
2. To assess the safety and tolerability of favipiravir in this subject population.
3. To assess the development of antibodies against SARSCoV-2
4. To evaluate any changes in the PK profile of favipiravir and its major metabolite M1 in this subject population
5. To determine the viral load and duration of viral shedding in stool as measured by RT-PCR.

6. To characterize microbiome signatures of infection by next-generation sequencing.

5 SUBJECT POPULATION

5.1 Inclusion Criteria

The following criteria must be confirmed as "YES" except optional PK, antibody, and stool sample collection:

1. Adults (18 to 80 years old inclusive)
2. Diagnosis of COVID-19 disease:
    a. If symptomatic without signs of respiratory distress (as defined by SpO2 >=94% on room air, RR <=20, HR <=100), with FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 within 72 hours from swab to the time of commencing informed consent. Mild disease is defined as having at least 1of the following:
        i. Fever (>98.7F)
    b. Cough/Shortness of breath/dyspnea
    c. Fatigue
    d. Headache/Body aches
    e. Joint pain
    f. Chest pressure
    g. GI symptoms including nausea, vomiting, and/or diarrhea
    h. Abdominal pain
    i. Sore throat
    j. Nasal congestion
    k. Chills
    l. Runny nose
    m. New loss of taste or smell
    n. Abdominal pain
    o. Rash
    p. If asymptomatic, initial diagnosis obtained no more than 72 hours from initial swab to the time of commencing informed consent
3. Subject or their legal representative understands the requirements of the study and provides written informed consent prior to undergoing any treatment-related procedures.
4. Subject agrees to take daily nasal swabs (anterior nares) for Day 1 to Day 10 and Day 14, 21, and 28 using the study provided materials, and mail via FEDEX each sample on the day collected.
5. Subject agrees to record daily symptoms, temperature, oxygen saturation, and pulse using the study provided materials.
6. Subject agrees to obtain stool samples after the Day 1 visit, and 1-3 days before the Day 14 and Day 28 timepoints and agrees to bring the sample back in the provided stool collection kit to their subsequent appointment and to optionally mail in 4-month sample. Collection of stool is optional for sites.
7. Subject agrees to return to the study site for follow-up visits on Day 5, 10, and 28. The study site will be staffed by trained healthcare providers wearing full personal protective equipment and study site equipment will be disinfected between patients according to the same protocols

as a clinical setting. Subjects will be wearing masks, will be appropriately spaced, and the number of subjects assessed at each time will be limited.

8. Subject agrees to maintain home or other quarantine as recommended by the study physician, except to visit the study site as required by the protocol.
9. Members of the same household may participate in the study as long as the inclusion and exclusion criteria are met.
10. 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).
11. 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 urine 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, as defined by positive respiratory culture
2. Subject has a history of abnormalities of uric acid metabolism unless cleared
3. Subject has a history of hypersensitivity to an anti-viral nucleoside-analog drug targeting a viral RNA polymerase
4. Subject has any of the following abnormal laboratory test results at screening:
    a. Platelet count <100,000 cells/mm^3
    b. Absolute lymphocyte count <500 cells/mm^3

c. Hemoglobin <11 g/dL for women and <12 g/dL for men
d. Serum creatinine concentration ≥1.5× ULN
e. Confirmed creatinine clearance (CrCl) < 50 mL/min by Cockcroft-Gault
f. Serum uric acid >20mg/dL

5. 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. 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.

6. 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 per investigator judgement).
7. Has previously received favipiravir within the past 30 days.
8. Has renal insufficiency requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
9. Has liver impairment greater than Child-Pugh A. (NOTE: Child-Pugh A subjects will have the maintenance dose decreased to 800 mg BIID).
10. Has a history of alcohol or drug abuse in the previous 6 months.
11. Has a psychiatric disease that is not well controlled where controlled is defined as: stable on a regimen for more than one year.
12. Has taken another investigational drug within the past 30 days.
13. 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.
- AST or ALT > 8 x ULN
- ALT or AST > 3 x ULN AND total bilirubin > 2X ULN
- AST or ALT > 3 x ULN AND patient has right upper quadrant pain or eosinophilia

- Uric acid >20mg/dL CrCl < 30

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

5.4 Compensation

Compensation, if any, may be determined locally and in accordance with local IRB requirements and approval.

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

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 800 mg twice daily BID (Ideally 12 hours apart but 10- 16 hours is allowed) on Days 2-10 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 600 mg BID on Days 2 through 10.

Subjects randomized to the placebo + SOC arm will be administered placebo BID (ideally 12 hours apart but 10-16 hours is allowed) on Day 1, and then maintenance dosing twice daily BID (Ideally 12 hours apart but 10- 16 hours is allowed) on Days 2-10 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.

6.2 Administration of Favipiravir or placebo

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.

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

6.3 Outpatient Favipiravir Dosing

Subjects in the favipiravir + SOC arm, will be dispensed sufficient favipiravir to ensure continued dosing until their next study visit. Subjects in the placebo+ SOC arm, will be dispensed sufficient placebo to ensure continued dosing until their next study visit. Subjects in both arms 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.
4) The intention is to complete a 10-day course of medication. If, because of missed doses, there are leftover doses after completing their PM dose on Day 10, bring all additional doses to their next study visit.

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 designee) 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).

The following message appears on the daily questionnaire given to subjects with favipiravir to take at home:

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 before you started the trial, 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 14: 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 11.c, obtain urine pregnancy test and proceed it result is negative.
- Measure and record vital signs (BP, HR, Temp, Resp).
- Collect and record SPO2 by Finger Sensor
- Perform Physical exam (may be done by the Principal Investigator or their designee)
- Complete baseline symptom survey to establish severity of symptoms (if present)
- Collect oropharyngeal swab for virologic testing (RT-PCR) and resistance analysis.
- Collect two nasal swabs for antigen testing and molecular viability testing.
- Collect blood samples for
  - Uric acid
  - CRP
  - Hematology and clinical chemistry laboratory analyses (samples collected within 48 hours of enrollment are acceptable):
  - Resistance analysis
  - Optional: Antibodies to SARS-CoV-2.
  - Optional: Biobanking
  - Optional: Pre-dose PK

- Perform subject randomization (via EDC) to establish treatment arm (favipiravir + SOC or placebo + SOC).
- Explain in home procedures for the study (self-sampling of nasal swabs, temperature, SPO2, completing the daily questionnaire and the optional collection of stool sample).
- Provide supplies to research subject and review the calendar of return visits.
- Optional: Explain that stool sample from first bowel movement after enrollment should be collected in Zymo fecal tube and brought back to Day 5 follow-up visit. If the first bowel movement sample cannot be collected, it is permitted to collect a subsequent bowel movement sample.

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 favipiravir or placebo) at time 0.

Following First Dose:

- Monitor patient for 30 minutes after their first dose.
- Optional: Take a blood sample 45 to 75 minutes following the first dose for post-dose PK analysis

7.3 Days 5, 10, 28 (Follow-up) or Early Termination (Window of +1 or -1 day allowed on Days 5 and 28. Window of -1 allowed for Day 10.)

- Conduct and record the results of a Physical Exam (Day 5, 10, 28).
- 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 oropharyngeal swab for virologic testing (RT-PCR) and resistance analysis.
- Collect and record adverse events (see Section 8.4 for detailed instructions).
- Collect nasal swab for antigen testing and molecular viability testing (day 1, 5, 10)
- Collect blood samples for:
  - Hematology and clinical chemistry laboratory analyses (Day 5, 10, 28)
  - Urine for repeat pregnancy test (Day 5)
  - Optional: Antibodies to SARS-CoV-2. (28)
  - Optional: Biobanking (28)
  - Optional: Blood for PK and resistance analysis obtained pre-dose (within 30 minutes prior to dosing) and post-dose (45 to 75 minutes following dosing) (Days 5 and 10).
- Optional: Provide Zymo fecal stool collection kit: one on Day 1, two on Day 10, and 28.

- Optional: Collect stool samples on Day 5, 14, 28, and patient sends in sample at 4 months post enrollment date.

8 EFFICACY, PHARMACOKINETICS AND SAFETY ASSESSMENTS

8.1 Efficacy Assessments

Primary Measurement (Efficacy):

1. Nasal swab for PCR taken daily from Day 1 to Day 10, and Days 14, 21, and 28.

Secondary Measurements (Efficacy):

1. Nucleic acid (RT-PCR) from oropharyngeal swabs collected on Days 1, 5, 10, and 28.
2. Symptom improvement or worsening: Subjects will fill in a diary daily, recording the following symptoms:
    a. Cough/Shortness of breath/dyspnea
    b. Fatigue
    c. Headache/Body aches
    d. Joint pain
    e. Chest pressure
    f. GI symptoms including nausea, vomiting, and/or diarrhea
    g. Abdominal pain
    h. Sore throat
    i. Nasal congestion
    j. Chills
    k. Runny nose
    l. Oral temperature taken after 4 pm and at least four hours after ingesting the most recent antipyretic (acetaminophen or NSAID)
    m.
    n. New loss of taste or smell
    o. Abdominal pain
    p. Rash
3. Blood for determination of antibodies to SARS-CoV-2 will be obtained on Days 1, 14, and 28.
4. Number of subject hospitalizations, emergency department visits, incidence of respiratory failure, deaths, and proportions of subjects alive, not hospitalized, and free of respiratory failure on day 28

8.2 Required Resistance Testing

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

8.3 Pharmacokinetics/Pharmacodynamics Assessments

6.0mL of blood may be collected for PK obtained pre-dose (within 30 minutes prior to dosing) and post-dose (45 to 75 minutes following dosing) on Days 1, 5 and 10. These collections are optional.

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)	Albumin
Glucose	Bicarbonate
Total protein	Sodium
Phosphate	Chloride
Potassium	
Calcium	C-reactive protein
Urate	

NOTES:

- All clinical laboratory assessments listed above (hematology and chemistry) will be conducted at the Stanford University Medical Center 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 up to 7 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 28 days post-treatment.

Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Site Investigator (and/or designee) must document all AEs reported through completion of the Day 28 visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has resolved or stabilized or 14 days after last dose, if in the

favipiravir arm. The Site 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 Placebo + SOC arm, must be recorded as an AE or SAE (if applicable), on the Adverse Event eCRF and SAE form, as applicable. The Site Investigator must follow all AEs until the AE resolves, or until the Site 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 Site 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 Site 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 Site 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 initially by the Site 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).

Final determination of relatedness will be made by the Sponsor.

Expectedness: Whether or not the event was excepted or unexpected. Further details on this can be found in section 8.5.

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 46 days post-dose must be reported to the Sponsor as soon as the site becomes aware of them. Any SAEs occurring more than 46 days after last 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 Site 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 with a minimum one overnight stay. 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 Site 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 (or designee) will distribute completed SAE forms, which may be used to notify the IRB when applicable, via a secure internet-based document depository.
- The Site Investigator should notify the IRB of Serious Adverse Events occurring at the site and other adverse reports received from the Sponsor in accordance with reporting requirements of the governing IRB.

The Site 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. However, treatment medication should only be recorded in the narrative description section of the SAE form.

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 a Site 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 Site 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 Sponsor determines the information qualifies for reporting and are counted in calendar days – not business days. Therefore, it is important that the Site 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

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.

9.1 General Considerations

For the primary comparison, the following will be tested:

- Null hypothesis: time to cessation of oral shedding is equal in control and treatment;
- Alternative hypothesis: time to cessation of oral shedding differs between control and treatment.

Hypothesis tests will be two sided and conducted at an overall alpha = 0.05 level of significance.

The number of hospitalizations and emergency department visits will be estimated for each arm, with 95% confidence intervals. The frequency of adverse events and serious adverse events will be

tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

9.2 Sample size justification

Approximately 180 patients will be enrolled.

Assuming 1:1 randomization and the use of a two-sided log rank test at the alpha=0.04999 level of significance for the final analysis, 79 events will provide 80% power to detect a hazard ratio of 2.03. This leaves alpha=0.00001 to check for overwhelming efficacy after 60 participants have completed 24 hours of follow-up. Assuming the control and treatment arm median cessation of shedding is 14 and 7 days, respectively, a two-month accrual period, a two-week follow-up period after randomization of the last patient, and a drop out of 10% in the control arm, it is estimated that the total sample size required to achieve 79 events is 120 (60 patients in each arm). We assume 33% of patients will test negative for SARS-CoV-2 virus by RT-PCR on Day 1, thus the total sample size required to be randomized is 180 (120/0.67). The assumption of 33% is based on calculations performed after the DSMB recommended a sample size re-estimation to account for the patients who test negative at baseline and do not contribute meaningfully to the primary analysis.

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:

The intent-to-treat (ITT) population will include all randomized patients. Patients will be analyzed according to their assigned treatment arm. All efficacy analyses will be completed in the ITT population.

The safety population will include all patients who receive study treatment. Patients will be analyzed according to actual treatment received. All safety analyses will be completed in the safety population.

9.5 Stratification, Subgroup Analysis and Pooled Analysis

Following consent, those subjects meeting all entry criteria will be randomized in a 1:1 ratio

Treatment Arm: favipiravir + SOC

Control Arm: placebo + SOC

Randomization will be stratified by age (>=50 and <50 years old) and sex.

Members of the same household may participate in the study as long as the inclusion and exclusion criteria are met. Because this is a double-blind, placebo-controlled trial, subjects from the same household will be randomized just as any other subject.

9.6 Efficacy Endpoint Analysis

Descriptive analyses

Descriptive statistics (proportions for categorical variables, means, medians, standard deviations, and interquartile ranges for continuous variables) will be reported for all key patient variables, including baseline and demographic characteristics, use of medications, compliance, and study completion status. Data that are missing on key patient characteristics and the outcome will be fully described, including any patterns of missingness (i.e., any relationships between missingness of a variable and patient characteristics).

A CONSORT diagram displaying the number of patients screened, eligible, and consented along with reasons for ineligibility will be provided. Graphical tools such as histograms, boxplots, and scatterplots will be created to assess quality of data and to display patterns over time.

Primary efficacy analysis

Time until shedding cessation will be compared between the two treatment arms using a Cox proportional hazards model adjusted for age and sex and stratified by site. The test will be performed at the alpha = 0.05 level of significance. The hazard ratio for shedding cessation will be estimated, along with its 95% confidence interval, from a Cox proportional hazards model. If the proportional hazards assumption is not met, we will consider an extended Cox model that relaxes the proportional hazards assumption.

The distribution of shedding cessation will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to shedding cessation at the end of the study period along with 95% confidence intervals will be presented for each treatment arm.

Secondary efficacy analyses

The distribution of cessation of symptoms will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment arm. Time to cessation of symptoms at the end of the study period along with 95% confidence intervals will be presented for each treatment arm. The hazard ratio for cessation of symptoms will be estimated, along with its 95% confidence intervals, from a Cox proportional hazards model. Time to cessation of symptoms will be determined by analysis of daily questionnaires. Resolution of symptoms requires that symptoms are mild or absent for at least 24 hours.

The number of hospitalizations, emergency department visits, incidence of respiratory failure, deaths, and proportions of subjects alive, not hospitalized, and free of respiratory failure will be estimated for each arm, with 95% confidence intervals. Respiratory failure is defined as the need for mechanical ventilation, ECMO, non- invasive ventilation, or high-flow oxygen

Our analyses will use multiple imputation methods that assume data are missing at random by including all baseline characteristics, treatment assignment, and reasons for missingness in the imputation model. This approach will be applied to any analysis involving endpoints or key variables where any missing data occurs in order to adhere to the ITT principle. Assumptions regarding missingness will be addressed in sensitivity analyses.

9.7 Safety Analysis

The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

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 28 days post-treatment. 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 INTERIM ANALYSIS

An interim analysis for safety and overwhelming efficacy will be performed once 50% of patients have 24 hours of follow-up complete. Enrollment will pause once 50% of patients have received treatment and will remain paused until the DSMC makes their recommendation after their safety review. The DSMC will meet one or two days after enrollment is paused to review the safety data collected within the first 24 hours of follow-up on all enrolled patients. We additionally expect blood count labs collected at day 5 to be available in approximately 25% of patients at the time of the DSMC review.

The DSMC will also review the efficacy data on all randomized participants at this meeting. The interim efficacy analysis will use the same methods as are planned for the final analysis using the ITT analysis. Based on the results of the interim analysis, the DSMC will either recommend to the sponsor to terminate the study for overwhelming efficacy ($p<0.00001$ at the interim analysis),

terminate the study for safety concerns, modify the study, or continue the study as planned. No formal stopping rules for futility are planned.

11 RECORDING AND COLLECTION OF DATA

11.1 Case Report Form

The Investigator or designee will record all data collected on the electronic Case Report Form (eCRF) provided for that purpose. For this study, REDCAP cloud will be the eCRF. 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.

11.2 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.

11.3 Monitoring

Due to the restrictions imposed on clinical and hospital visits by the COVID-19 pandemic, most monitoring activities of this study will be conducted remotely. Monitors will work with the site

study staff at each site to determine times for "joint" remote or in-person monitoring – meaning that the monitor and the site study staff will review data together.

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 site study staff will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of monitoring and by prompt attention to any matters brought to their attention by the monitor.

11.4 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 site Investigator and site 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.

11.5 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.

12 ETHICS

12.1 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.

12.2 Subject Information and Consent

It is the responsibility of the site 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 receive compassionate treatment. A copy of the ICF, signed and dated by the subject/representative and the site 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.

13 GENERAL CONSIDERATIONS

13.1 Discontinuation of the Study

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

13.2 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.

14 SCHEDULE OF ASSESSMENTS

Day	Assessment in the study clinic	Administration of study drugs	Self-collected nasal swab and self-assessment)	Oropharyngeal swab	Blood collected by phlebotomy for clinical labs (CBC, Chem 7, LFTs, uric acid, CRP)[A, B]	Blood collected by phlebotomy for biobanking/ immunology studies [C]	Blood collected by phlebotomy for PK, pre- and post-dose [C]	Urine for pregnancy test (serum if needed)	Stool self-collected using Zymo fecal kit, [C]	Collect nasal swabs for antigen testing	Collect nasal swab for molecular testing
1	X	X	X	X	X	X	X	X	Dispense stool kit	X	X
2		X	X								
3		X	X								
4		X	X								
5	X	X	X	X	X		X	X	X	X	X
6		X	X								
7		X	X								
8		X	X								
9		X	X								
10	X	X	X	X	X		X		Dispense two stool kits	X	X
14			X						X		
21			X								
28	X		X	X	X	X			X, Dispense stool kit		

Appendix A: Subject Status

A: Blood for uric acid and CRP required at Day 1 while results for CBC/Chem 7/LFTs can be within 48 hours of enrollment
B: Local lab ranges will be submitted by sites for review prior to initiation
C: Collection of biobanking, PK, and stool are optional for sites.

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

See symptom survey