CLINICAL STUDY PROTOCOL

FAVIPIRAVIR in COVID-19
Effect on viral shedding and disease progression

The **Pre**vent **Se**vere **CO**VID-19 (**PRESECO**) Study

Protocol Number: ATI0220

Protocol Version: 5.1
Date: 02 November 2021

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Signatures of Approval of Protocol

This protocol was subject to critical review and has been approved by the following persons:

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1.0 STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following and any other applicable local regulatory bodies:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

- Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária (ANVISA)* Regulations applicable to clinical studies (Law No.782, Resolution No.9, Resolution No.61 and Resolution No.176)

Clinical trial staff who are responsible for the conduct, management, or oversight of this study should have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the appropriate Institutional Review Board /Independent Ethics Committee (IRB/IEC) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. In addition, all changes to the consent form will be IRB/IEC-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

INVESTIGATOR'S STATEMENT

Study title: "Double-blinded, placebo control, randomized, phase-3 clinical trial to evaluate clinical efficacy of Favipiravir in patients with mild to moderate symptoms related to COVID-19 infection"

The signature below:

- Confirms my agreement to conduct the trial in compliance with Good Clinical Practice (GCP), applicable regulatory, and the clinical study protocol requirements,
- Confirms my agreement to comply with the procedures for data recording and reporting,
- Confirms my agreement to permit monitoring, auditing and regulatory inspections,
- Confirms my agreement to retain the study essential documents in investigator file until Appili Therapeutics informs me these documents are no longer needed (e.g. over 15 years),
- Ensure all the persons assisting with the study are adequately informed about protocol, the investigational product(s), and their trial related duties and functions,
- Confirms that I have read this protocol and I agree to comply with all parts or items.

All information regarding this protocol and the investigational product(s) will be treated as strictly confidential.

Trial site name and full address:

Principal Investigator's Name:

_____

Signature with date

2.0 PROTOCOL SUMMARY

2.1 Protocol Synopsis

Long Title	Double-blinded, placebo control, randomized, phase-3 clinical trial to evaluate clinical efficacy of Favipiravir in patients with mild to moderate symptoms related to COVID-19 infection
Short title	Favipiravir to shorten the time to sustained clinical recovery
Protocol No.	ATI0220
Version	5.1 dated 02-November-2021
Background	COVID-19 starts as a pure viral infection and evolves into a multifactorial disease with components of hyper immune activation, end organ damage, and fibrosis. Suppression of viral replication is expected to be impactful early in the course of disease. The ability to mitigate the symptoms at an early stage will prevent progression to severe COVID-19 and can save many lives. Early treatment could also reduce viral shedding, diminishing the period of infectivity and decreasing the number of secondary cases.
Study design	Double-blinded, placebo controlled, randomized, phase 3 trial evaluating the antiviral drug favipiravir as potential therapy for mild to moderate COVID-19 in adult outpatients who are not requiring hospitalization and who had a positive COVID-19 test within 72 hours of study enrollment. Mild to moderate symptoms are defined as: O_2 Saturation $\geq$94%, no requirement of supplemental O_2, lack of known sepsis or organ failure. Subjects will be randomly assigned to favipiravir (the first two doses are 1800 mg given approximately 12 hours apart, followed by 800mg approximately every 12 hours to complete 10 days of therapy) or placebo.
Favipiravir	A selective inhibitor of viral RNA-dependent RNA polymerase (RdRP) with potent antiviral activity against single-stranded RNA viruses including coronaviruses. It is indicated in the treatment of influenza in Japan and China and COVID-19 in Russia and India.
Sample size	The entire study: approximately 1250 (approximately 625 subjects per treatment arm) are estimated to be sufficient to get 815 sustained clinical recoveries. The viral shedding sub-study: approximately 550 (approximately 275 per arm) to obtain 112 viral shedding events.
Primary Study Objective	• Demonstrate that treatment with favipiravir for COVID-19 patients with mild to moderate symptoms will shorten the time to sustained clinical recovery (‘clinical endpoint component’) compared to placebo.
Study Secondary Objective	• Demonstrate that treatment with favipiravir will shorten the period of viral shedding (‘viral shedding component’) compared to placebo

	• Demonstrate that treatment with favipiravir will reduce the proportion of subjects with COVID-19 related hospitalizations or emergency department visits compared to placebo • Demonstrate that treatment with favipiravir will reduce the proportion of subjects with COVID-19 related hospitalizations or emergency department visits or the development of two or more new COVID-19 related symptoms compared to placebo
Endpoints	**Symptom Assessment:** A patient-reported outcome (PRO) instrument will be used to assess COVID-19-related symptoms (measuring signs and symptoms best known by the patient and measured from the patient perspective). The assessment will be performed every 24 hours at approximately the same time each day. The following symptoms will be included in the daily assessment (regardless of which symptoms the subject had at baseline, as new symptoms may appear following the baseline assessment): a. Stuffy or runny nose, sore throat, shortness of breath, cough, lack of energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea: subjects rate symptom at its worst over a 24-hour period using a 4-point scale for severity- 0=none, 1=mild, 2=moderate, 3=severe b. Vomiting, diarrhea: subjects rate symptom frequency over a 24-hour period using a 4-point scale for frequency- 0= not at all, 1=1–2 times, 2=3–4 times, 3=5 or more times c. Sense of taste, sense of smell (not included in the Primary Endpoint assessment): subjects rate symptom over a 24-hour period using a 3-point scale- 0= sense (of smell or taste) is the same as usual, 1= sense is less than usual, 2=have no sense **Primary Efficacy Endpoint:** Time to Sustained Clinical Recovery defined as number of days from start of study treatment to Sustained Alleviation of Symptoms, evaluated from study day 1 onward. The endpoint will be considered to have been met at the earliest time point, starting on study day 1, at which the subject has reached Sustained Alleviation of Symptoms as defined by: (1) Blood oxygen saturation ≥94% on room air at rest, (2) Oral temperature <38.0 ºC AND (3) All COVID-19 associated symptoms (stuffy or runny nose, feeling hot or feverish, chills or shivering, cough, sore throat, lack of energy or tiredness, nausea, headache, muscle or body aches, shortness of breath, vomiting, diarrhea) (Symptoms related to smell or taste are not included in the primary endpoint) reported by the patient have reached a severity of "0 – none" or "1 – mild" in assessments for 4-point scale assessments and not known to have redeveloped any COVID-19 associated signs and symptoms (not including reduced sense of taste or smell) in a severity beyond mild for 4 consecutive days (inclusive of the day when clinical recovery was achieved) when assessed from the start of study treatment to day 28. To meet the primary endpoint, subjects must survive with no hospitalization to day 28. **Key Secondary Efficacy Endpoint:**

- Proportion of subjects with COVID-19 progression, where progression is defined as the occurrence from study day 1 onward of any emergency department (ED) visit for COVID-19 worsening or shortness of breath **OR** hospitalization for COVID-19 worsening or shortness of breath **OR** death (narrow progression)

- Proportion of subjects with COVID-19 progression, defined as the occurrence from study day 1 onward of any ED visit for COVID worsening or shortness of breath OR hospitalization for COVID worsening or shortness of breath OR death OR the development of symptomatic worsening from study day 1 onward (defined as ≥2 additional COVID symptoms at a level of moderate or severe which have not existed (at any level of severity) at baseline or fever (temperature of ≥38.0ºC) which has not existed at baseline or oxygen desaturation (O2 saturation <94%) which has not existed at baseline) (Broad progression).

- Viral Shedding Sub-Study:
  Time (number of days) to conversion (defined as undetectable viral load) of detectable SARS-CoV-2 viral RNA in RT-PCR assays of saliva, from start of study treatment to date of last viral assessment. Included: all subjects with a positive PCR on study day 1 or 2 or 3. The endpoint will be assessed from study day 1 onward.

Additional Secondary Efficacy Endpoints

Time (number of days) to negative conversion of positive SARS-CoV-2 viral culture assays of saliva, from start of study treatment to date of last viral assessment. Subjects with a positive saliva SARS-CoV-2 PCR on any study day will have viral cultures performed. Subjects with a positive viral culture on day 1 or 2 or 3 will be included in this analysis. The endpoint will be assessed from study day 1 onward.

Exploratory Endpoints:

- Proportion of subjects showing sustained clinical recovery by study Day 1, 3, 5, 7, 10, 14, 21.
- Proportion of subjects showing resolution of symptoms by Days 1, 3, 5, 7, 10, 14, 21, where resolution is defined as symptom severity of 0 for all symptoms as well as temperature of <38.0 ºC as well as oxygen saturation of ≥94%.
- Proportion of patients showing negative conversion of detectable SARS-CoV-2 viral RNA (defined as SARS-CoV-2 viral load conversion from detectable on study day 1 or 2 or 3 to undetectable thereafter) in saliva on Study Days 3, 5, 7 and 10. Included: all subjects with a positive PCR (defined as detectable viral load) on study day 1 or 2 or 3.
- Proportion of patients showing negative conversion of positive SARS-CoV-2 viral culture in saliva on Study Days 3, 5, 7, and 10. Subjects with a positive saliva SARS-CoV-2 PCR on any study day will have viral cultures performed. Subjects with a positive viral culture on day 1 or 2 or 3 will be included in this analysis.

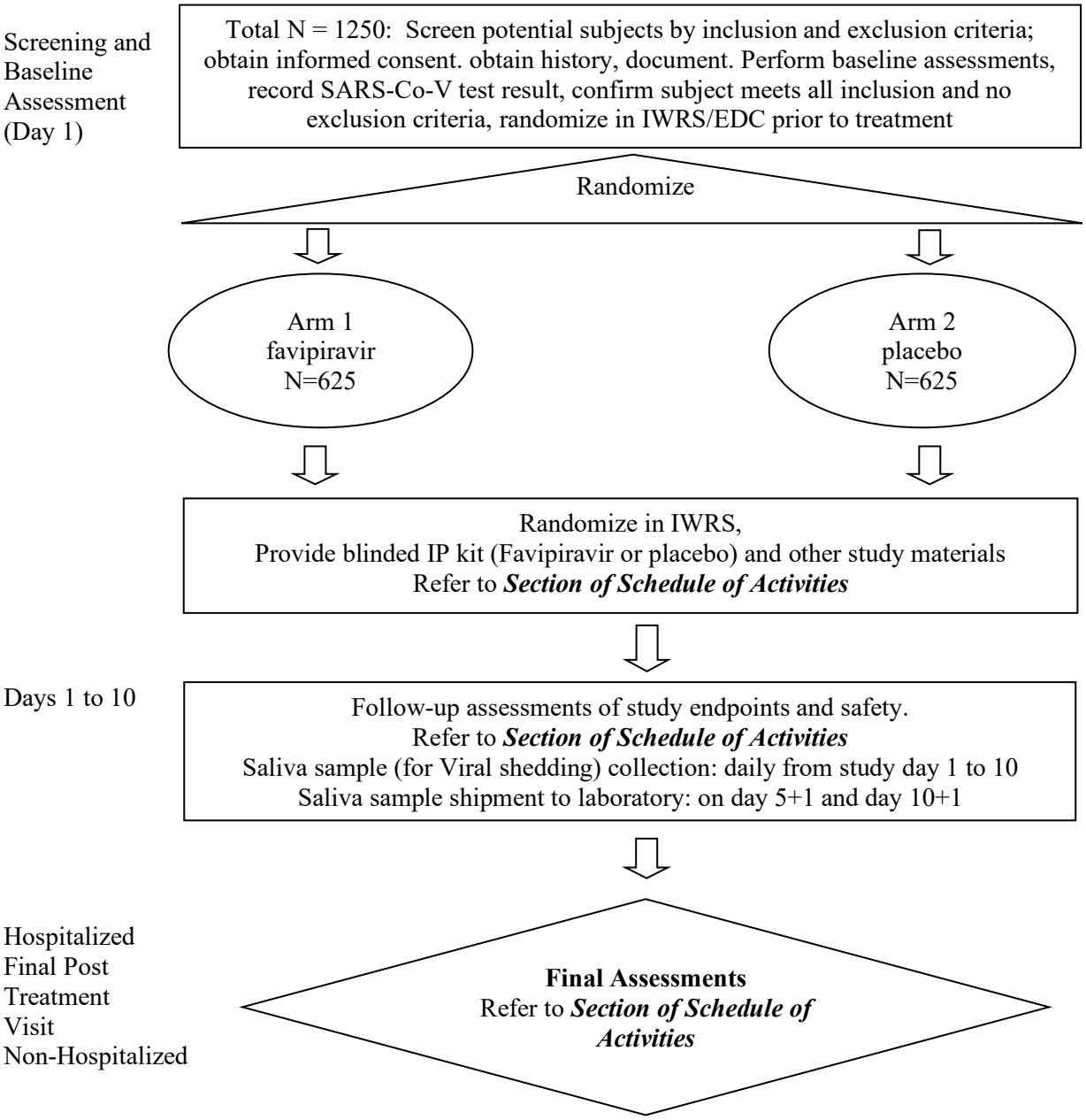
	• Proportion of subjects dying from any cause over an assessment period from start of study treatment until Day 28. • Proportion of subjects requiring mechanical ventilation over an assessment period from start of study treatment until Day 28. • Time (number of days) to negative conversion (defined as viral load <100 copies) of detectable SARS-CoV-2 viral RNA (defined as viral load ≥100 copies) in RT-PCR assays of saliva, from start of study treatment to study day 10. Included: all subjects with a positive PCR on study day 1 or 2 or 3. The endpoint will be assessed from study day 3 onward. • Time to Sustained Clinical Recovery defined as number of days from start of study treatment to Sustained Alleviation of Symptoms, evaluated from study day 3 onward. • Proportion of subject with COVID-19 progression, where progression is defined as the occurrence at any point from study day 1 to study day 28 of emergency department (ED) visit for any reason **OR** hospitalization for any reason. • Proportion of subjects with COVID-19 progression, where progression is defined as the occurrence from study day 3 onward of any emergency department (ED) visit for COVID-19 worsening or shortness of breath **OR** hospitalization for COVID-19 worsening or shortness of breath **OR** death (narrow progression) • Proportion of subjects with COVID-19 progression, defined as the occurrence from study day 3 onward of any ED visit for COVID worsening or shortness of breath OR hospitalization for COVID worsening or shortness of breath OR death OR the development of symptomatic worsening from study day 3 onward (defined as ≥2 additional COVID symptoms at a level of moderate or severe which have not existed (at any level of severity) at baseline or fever (temperature of ≥38.0ºC) which has not existed at baseline or oxygen desaturation (O2 saturation <94%) which has not existed at baseline) (Broad progression). **Safety endpoint:** • Number (and proportion) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term). • Number (and proportion) of patients reporting serious treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term). • Vital Signs including oral temperature, heart rate, oxygen saturation with height and weight. • Clinical laboratory tests including Biomarkers, Chemistry, Coagulation and Hematology.
Study duration	• Individual subject will complete all the study visits within 28 days of enrollment.

	• Adverse events will be monitored and collected by the Study Team from the point of signed consent until study day 28.
Study sites/ facilities	• COVID-19 testing centers • COVID-19 testing laboratories • Clinic/Hospital/Treatment Centre/Research Center • Subjects' home • Besides study visits on Day 1 and Day 10 which will be in-person in-study site or at the subject's home, all other study procedures do not require in-person interaction and will be done remotely, using telehealth and video conferencing. Study materials will be provided to the subject at the study site or at the subjects' home.
Enrollment strategy	• Study candidates will be identified at COVID testing centers, COVID testing laboratories, and in other clinical care settings. • Tested individuals who are ≥18 years will be asked at the testing center or at the time of receiving a positive test result or when seen at a care center for suspected or confirmed COVID-19 for a verbal consent to be approached by the study team. • Study team member will inform study candidates about the study and probe their interest in participating. If interested, study subjects will be screened for inclusion and exclusion criteria. If qualified for enrollment, an in-person visit will be scheduled. • Enrollment of subjects age 18-30 without underlying medical conditions will be capped at 40% • The viral shedding sub-study will include approximately 550 subjects to be enrolled into the trial
Inclusion criteria	Study subjects should meet all of the following criteria: 1. Adults age 18 or older 2. Tested positive for SARS-CoV-2 by RT-PCR assay or by Rapid Antigen assay (first positive test) using a respiratory tract sample (either nasopharyngeal swab OR oropharyngeal swab OR nasal aspirate OR tracheobronchial aspirate OR saliva) collected within 72 hours of randomization 3. Stated willingness to give their written informed consent to participate in the study 4. Stated willingness to comply with all study procedures and availability for the duration of the study 5. Males must be sterile, OR agree not to donate semen AND agree to strictly adhere to contraceptive measures (e.g. condom use) during the study and for 7 days following the last dose of study medication 6. Females must be unable to bear children, OR ensure that their male partner is incapable of fathering a child, OR, if of childbearing potential will strictly adhere

	to contraceptive measures during the study and for seven days following the last dose of study medication (as detailed in section 5.8) 7. Females must agree to stop breast-feeding prior to first dose of study drug and through seven days after completing therapy 8. Females must have a negative pregnancy test at screening 9. Ability to take oral medication and be willing to adhere to the favipiravir/placebo regimen 10. Minimal baseline severity score for COVID-19-related symptoms: at least two symptoms with a score of 2 or higher. COVID-19-related symptoms include: Stuffy or runny nose, sore throat, shortness of breath, cough, lack of energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, diarrhea, vomiting (Excluding changes in the sense of taste or smell) 11. Subject has access to a smart phone, tablet or PC
Exclusion Criteria	An individual who meets any of the following criteria will be excluded from participation in this study: 1. O_2 saturation <94% 2. Shortness of breath at rest 3. Heart rate ≥ 125 per minute 4. COVID-19 symptoms first presented >5 days prior to randomization 5. Requirement for hospitalization at the time of enrollment 6. Participation in another trial or use of any experimental treatment for COVID-19 7. Treatment with high steroid dose i.e. >30 mg/day prednisolone equivalent (excluding stable chronic treatment) or remdesivir or anyone receiving SARS-CoV-2 monoclonal antibodies within 3 months prior to enrollment 8. Known sepsis or organ dysfunction/ failure 9. Known infection with a respiratory virus other than SARS-CoV2 (e.g. Influenza) or any known bacterial infection (affecting the respiratory system or any other system) 10. Inability to adhere to study requirements 11. For premenopausal women: unwilling or unable to use effective birth control measures 12. Known allergy to favipiravir 13. Known end-stage kidney disease or requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) 14. Known liver impairment greater than Child-Pugh A 15. Psychiatric illness that is not well controlled (defined as stable on a regimen for more than one year). 16. Known elevated uric acid levels in the past year or taking uric acid lowering medications (allopurinol, febuxostat) 17. History of hereditary xanthinuria or history of xanthine urolithiasis. 18. History of gout or actively being treated for gout.

	19. Current use of the following medications, which cannot be discontinued for the duration of the study: pyrazinamide, hydralazine, more than 3000 mg of acetaminophen per day.
Study evaluations	Subjects will be followed for symptoms and signs of infection (until study day 28), adverse events (any AEs: until study day 14, SAEs: until study day 28), and viral shedding (daily from study day 1 to 10).
Statistical plan	• The primary analysis population is the mITT population, which includes all randomized subjects who took at least 1 dose of study drug (excluding subjects who qualified for enrollment solely based on changes in smell or taste). For the primary efficacy endpoint of time to sustained clinical recovery, group sample sizes of approximately 625 subjects in each treatment arm (favipiravir and placebo) will achieve sufficient power to demonstrate a clinically meaningful difference using a two-sided Wilcoxon test at an overall significance level of 0.05. • An interim analysis will be performed to assess the safety of the patients, the efficacy endpoint for futility, the efficacy endpoint for treatment effect, and the progress of the trial and any medical consideration required to support patient's health and safety. The nominal alpha of 0.02 and of 0.0369, at the time of interim and final analysis, respectively. A p-value less than 0.02 (interim) or 0.0369 (final) will be considered to be statistically significant. Futility will be concluded at interim on the primary efficacy endpoint if Z-value is smaller than 0.58964 (i.e. p-value is larger than 0.6389). • For the viral shedding endpoint of time to undetectable viral shedding, group sample sizes of 275 subjects in each treatment arm will have sufficient power to detect a substantial effect size using a two-sided Wilcoxon test at a significance level of 0.05.

2.2 Scheme


Screening and Baseline Assessment (Day 1)
Total N = 1250: Screen potential subjects by inclusion and exclusion criteria; obtain informed consent. obtain history, document. Perform baseline assessments, record SARS-Co-V test result, confirm subject meets all inclusion and no exclusion criteria, randomize in IWRS/EDC prior to treatment
Randomize
Arm 1 favipiravir N=625
Arm 2 placebo N=625
Randomize in IWRS,
Provide blinded IP kit (Favipiravir or placebo) and other study materials
Refer to Section of Schedule of Activities
Days 1 to 10
Follow-up assessments of study endpoints and safety.
Refer to Section of Schedule of Activities
Saliva sample (for Viral shedding) collection: daily from study day 1 to 10
Saliva sample shipment to laboratory: on day 5+1 and day 10+1
Hospitalized Final Post Treatment Visit Non-Hospitalized
Final Assessments
Refer to Section of Schedule of Activities

2.3 Schedule of Activities (SoA)

Key activities [1]	Performed By	Screening & Baseline / Randomization / Treatment Day 1	Treatment Day 2	Treatment Day 3	Treatment Day 4	Treatment Day 5	Treatment Day 6	Treatment Day 7	Treatment Day 8	Treatment Day 9	Treatment Day 10	Post-Treatment Day 1	Post Treatment Day 2	Post-Treatment Day 3	Post-Treatment Day 4	Post-Treatment Days 5 to 6	Post-Treatment Day 7	Post-Treatment Days 8-10	Post-Treatment Day 11	Post-Treatment Days 12-13	Post-Treatment Day 14	Post-Treatment Days 15-17	Post-Treatment Day 18	Early Termination or Hospitalization
STUDY DAY		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 - 16**	**17**	**18 - 20**	**21**	**22 - 23**	**24**	**25 - 27**	**28**	
Informed Consent	Study Team	X																						
Confirmation of having a positive SARS-CoV2 test	Study Team	X																						
Record demographics (age, race, ethnicity, gender)	Study Team	X																						
Register in IWRS to allot subject screen number	Study Team	X																						
Review past medical and surgical history	Study Team	X																						
Record smoking, alcohol, medication history	Study Team	X																						
Record height and weight	Study Team	X[11]																						
Assess Inclusion/ Exclusion Criteria	Study Team	X																						
Randomization through IWRS to allot blinded IP kit number and also to assign randomization number	Study Team	X																						
Create ePRO credentials for the subject and help set-up the mobile app in subject's device	Study Team	X[9]																						
Blood tests [2]	Study Team	X									X													

Key activities [1]	Performed By	Screening & Baseline / Randomization / Treatment Day 1	Treatment Day 2	Treatment Day 3	Treatment Day 4	Treatment Day 5	Treatment Day 6	Treatment Day 7	Treatment Day 8	Treatment Day 9	Treatment Day 10	Post-Treatment Day 1	Post-Treatment Day 2	Post Treatment Day 3	Post-Treatment Day 4	Post-Treatment Days 5 to 6	Post-Treatment Day 7	Post-Treatment Days 8-10	Post-Treatment Day 11	Post-Treatment Days 12-13	Post-Treatment Day 14	Post-Treatment Days 15-17	Post-Treatment Day 18	Early Termination or Hospitalization
STUDY DAY		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15-16**	**17**	**18-20**	**21**	**22-23**	**24**	**25-27**	**28**	
Perform Urine Pregnancy Test for pre-menopausal women only (women of childbearing potential) and report	Subject	X[9]						X															X	X
Provide allotted Investigational product (IP) (favipiravir or Placebo) to subject	Study Team	X																						
Administration of IP (Favipiravir/Placebo) and report [3]	Subject	X[9]	X	X	X	X	X	X	X	X	X													
Report Concomitant Medications including OTC and herbal products	Subject	X	X	X	X	X	X	X	X	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]
Assess Concomitant Medications including OTC and herbal products[5]	Study Team	X		X		X		X		X	X				X		X		X		X		X	X
Assessment of IP adherence[5]	Study Team	X	X	X	X	X	X	X	X	X	X													
Report COVID-19 signs and symptoms [4]	Subject	X[9]	X	X	X	X	X	X	X	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]
Review and Assess COVID-19 signs and symptoms [5]	Study Team	X		X		X		X		X	X				X		X		X		X		X	X
Assess and report AE [5]	Study Team	X		X		X		X		X	X				X		X		X		X		X	X
Measure and report O_2 saturation, heart rate and oral temperature [5, 6]	Subject	X[9]	X	X	X	X	X	X	X	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]
Viral specimen (Saliva) collection and storage at subject's residence in room temperature [7]	Subject	X[9]	X	X	X	X	X	X	X	X	X													
Viral specimens (Saliva) shipment from subject's residence to laboratory [8]	Courier					X					X													

[1] If clinical evaluation is deemed not feasible due to subject's condition, the study team to collect Early Termination Visit data and attempt to complete the 21-day and 28-day follow-up call and AE assessment for those subjects who are hospitalized and deemed off study.

[2] CBC with differential, Electrolytes, BUN, Creatinine, Random Blood Serum Glucose, AST, ALT, Bilirubin, uric acid, SARS-CoV2 IgG, IL-6, IL-10, ESR, CRP, D-Dimer, ferritin. (CRP = C-reactive protein, IL-6 = Interleukin-6, IL-10 = Interleukin-10, CBC = Complete Blood Count). Site do not require to wait for blood test result to randomize subjects. For day 10 blood test, ±1 day window period is acceptable.

[3] The first two doses are 1800 mg taken approximately 12 hours apart, followed by 800 mg taken approximately every 12 hours to complete 10 days of therapy.

[4] During screening, record the number of days since the onset of COVID-19 symptoms

[5] The study team will be reviewing the data reported by subject to ensure compliance, accuracy and completeness on days 1, 3, 5, 7, 9, 10, 14, 17, 21, 24, and 28. Beyond Study Day 10, once the subject meets the primary efficacy endpoint, the subject is not required to continue the self-assessment and reporting of COVID-19 symptoms. However, the study team, during the remote patient visits will evaluate and report the severity of COVID-19 associated symptoms as per the set frequency mentioned in the table.

[6] Collect oximetry data once daily, with the caveat that if the daily O2 saturation result is 90-93%, the subject will repeat the measurement 2 hours later. If the result is <90%, the subject is instructed to contact the study team. The study team will decide if a recheck in 2 hours is appropriate or the subject needs further medical evaluation. Oral temperature will be measured twice daily. Heart rate will be measured once daily.

[7] Until the sub-study enrollment is completed, all subjects will be enrolled into the viral shedding sub-study. However, If they choose so, subjects can opt-out of participating in the viral shedding sub-study.

[8] 1st shipment on day 5 (+1) for all samples collected and 2nd shipment on day 10 (+1) for all the remaining collected samples. Saliva samples of 2nd shipment can be handed-over to site staff during the in-person site visit on day 10 (Site staff to ship it to laboratory).

[9] Activity to be performed at site with the help of site staff to ensure that the subjects are comfortable to perform at home by themselves from next day onwards.

[10] Beyond Study Day 10, once the subject meets the primary efficacy endpoint, the subject is not required to continue the self-assessment and reporting of COVID-19 symptoms and vitals. However, the study team, during the remote patient visits will evaluate and report the severity of COVID-19 associated symptoms and vitals as per the set frequency mentioned in the table. Data will be entered into ePRO from Day 1 to Day 10 irrespective of whether sustained clinical recovery is met or not.

[11] Height and weight should be collected at the screening visit. In cases where the data was not collected at the screening visit, the date of collection will be recorded.

3.0 INTRODUCTION

3.1 Study Rationale

The ongoing COVID-19 pandemic is an urgent public health crisis with few if any rapid and practical solutions. The outbreak of COVID-19 has been declared to be a public health emergency of international concern by the World Health Organization (WHO), and the development of effective therapies for fast-spreading fatal COVID-19 is in an urgent need [1]. Given the seriousness and time-sensitive nature of this highly contagious virus, the medical and scientific communities must work quickly and efficiently to find a feasible way to address this global emergency.

COVID-19 begins as pure viral infection, involving viral replication and virulence. Once progressed, it evolves into a multifactorial disease with components of viral infection, hyper immune activation, and end organ damage and fibrosis. In fact, many of those with progressed COVID-19 do not shed virus anymore and their course can be improved by reducing their immune responses using dexamethasone. Thus, the suppression of viral replication, i.e. antiviral effect, is expected to be most impactful early during COVID-19, when no or mild symptoms are present.

Unlike remdesivir, which is available only as IV and is therefore mostly limited to patients with severe COVID-19 that require hospitalization, favipiravir is available in a tablet form and can be used also in outpatients with asymptomatic or mild infection [2]. Progression from mild to severe COVID-19 is more frequent among older persons and those with certain underlying comorbidities. [3]. As a result, such populations contribute unproportionally to death from COVID-19 [4]. The ability to mitigate COVID-19 symptoms has the potential to decrease progression to severe COVID-19 and is of great importance as it has the potential to save many lives. In addition, early effective treatment is expected to shorten and reduce viral shedding [5]. Viral shedding in patients with symptomatic COVID-19 typically continues for 4-15 days, and sometimes >15 days. During this period, patients are considered to be infectious. Shortening the duration of viral shedding may decrease the risk of progression to severe COVID-19 and diminish the period of infectivity, thus possibly decreasing the number of secondary cases. Two small studies from China demonstrated that favipiravir decreases the period of viral shedding in symptomatic patients with COVID-19 [6-7].

3.2 Favipiravir: The study drug

At the time of writing, definitive therapies for established COVID-19 remain to be defined. Significant interest exists in repurposing existing antiviral agents for use against COVID-19. Favipiravir is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependent RNA polymerase [8-10]. It has activity against influenza A and B including activity against oseltamivir and zanamivir-resistant influenza viruses, several agents of viral hemorrhagic fever, and SARS-CoV-2 in vitro [11-13]. Favipiravir is approved for novel epidemic influenza strains unresponsive to standard antiviral therapies in Japan [14].

Favipiravir was identified to have activity in vitro against SARS-CoV-2, albeit a high concentration was required as compared to chloroquine or remdesivir (EC50 = 61.88 μM) [15]. Despite a similarly elevated EC50 identified for favipiravir and Ebola virus, it was identified in 14 previous animal models to be highly effective as post-exposure prophylaxis for mice exposed to an Ebola virus challenges, with rapid virologic response preventing mortality [16-18}. Based on the dosing strategies and pharmacokinetic data from human influenza trials, an intensified dosing strategy of 6000 mg loading on day 1 followed by 1200 mg

PO BID maintenance therapy for 10 days was employed in a single-arm clinical trial for Ebola virus disease in Guinea [19].

In a retrospective analysis of 124 patients with Ebola virus disease in Sierra Leone, those treated with favipiravir had a significantly higher survival rate compared to patients receiving supportive management (56% v. 35.3%, p=0.027) [20]. Patients received favipiravir 800 mg PO BID on day 1 and 600 mg PO BID for days 3-11. Viral loads were quantified for 35 patients twice during their hospitalization and were significantly reduced amongst patients receiving favipiravir.

Favipiravir has also been used as pharmacologic post-exposure prophylaxis for Ebola virus disease [21]. In a case series of four healthcare workers with higher risk Ebola virus exposures, including two hollow-bore needle stick injuries, none of the patients who received 10 days of high-dose favipiravir developed Ebola virus disease.

Early clinical experience with favipiravir for COVID-19 is promising. An open-label nonrandomized trial of 80 patients with COVID-19 in China identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared to historical controls treated with lopinavir/ritonavir [6]. Patients with mild or moderate COVID-19 were enrolled within 7 days from disease onset; those with severe or critical disease, ≥ 75 years old, chronic liver disease, or end-stage renal disease were excluded. Patients in the intervention arm received Favipiravir 1600 mg PO BID on day 1 followed by 600 mg PO BID on days 2-14. Both arms were co-treated with inhaled IFN- α1b 60 μg BID and therapy was continued until viral clearance, up to a maximum of 14 days. Thirty-five patients were assigned to favipiravir and 45 patients to lopinavir/ritonavir, with a median age of 47 (IQR 35.8-61); 13.7% were ≥ 65 years old. There was a significant reduction in the median time to viral clearance with favipiravir (4 days; IQR 2.5-9) as compared to lopinavir/ritonavir (11 days; IQR 8-13; p <0.001). Further, by day 14, 91.4% of patients in the favipiravir arm had radiographic improvement versus 62.2% of the lopinavir/ritonavir arm. There was a significantly lower rate of adverse events in patients receiving favipiravir (11.4% v. 55.6%, p<0.01).

In an open-label randomized trial in China, 240 patients with confirmed COVID-19 were randomized to favipiravir or arbidol [7]. Favipiravir was given at 1600 mg PO twice on day 1 followed by 600 mg PO BID until day 7-10. The clinical recovery rate by day 7 of treatment was higher amongst patients receiving favipiravir, albeit not achieving statistical significance (61.21% v. 51.67%, p=0.1396). Amongst patients with moderately severe disease, there was a significantly higher rate of clinical recovery by day 7 with favipiravir (71.43% v. 55.86%).

Top-line results are also available from an open-label, randomized, multicenter clinical trial recently conducted in 150 patients in India. Patients in the intervention arm received 1800 mg of Favipiravir PO twice daily on day 1 followed by 800 mg twice daily for up to a maximum of 14 days, along with standard supportive care. Randomization was stratified based on disease severity into mild (90 patients) and moderate (60 patients). The median time to cessation of oral viral shedding was 28.6% faster in the intervention arm although the difference was not statistically significant (Hazard Ratio 1.367 [95%CI 0.944,1.979]; p=0.129). Patients receiving favipiravir were reported to achieve clinical cure faster than controls and disease progression was delayed. No serious adverse events or deaths were reported in the intervention arm. Full study results have not yet been published.

In the current pandemic crisis, medical professionals are understandably focused more on stabilizing the very sick. However, if Favipiravir could work in any way to halt or prevent infection in the less sick (or even in the uninfected), it would be monumental in terms of returning to normal life. Because the drug has few side effects, taking Favipiravir prophylactically might help to prevent COVID-19 spreading. Even

if this treatment does not completely eradicate infection, Favipiravir treatment may help to decrease viral load, thereby allowing the host immune system to better combat the disease.

3.3 Favipiravir: Risk/Benefit Assessment

As of August 2020, more than 40 clinical studies with favipiravir have been conducted globally, mainly in the US and Japan. Favipiravir has been well tolerated in studies in adults and elderly subjects with uncomplicated influenza [22]. A consistent safety profile composed of relatively low frequencies of mild to moderate adverse events clustering around the system organ classes of gastrointestinal disorders has been characterized. Mild to moderate transient, asymptomatic elevations in serum uric acid and mild to moderate diarrhea are the two most common adverse events known to occur with favipiravir [2]. Favipiravir has been safely studied with therapy durations up to 22 days (JP120, Phase 1 study).

Favipiravir is considered a safe drug. No related serious adverse events occurred in licensure studies of favipiravir [23]. Preclinical and animal studies show no direct suppression of white blood cell types or immunosuppression by favipiravir. 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. Though an inhibitor of CYP 2C8 and aldehyde oxidase, few drugs are contra-indicated. Overall, the safety of favipiravir suggests that the potential benefit to human subjects exposed to a confirmed case of COVID-19 generally outweighs potential risks.

4.0 OBJECTIVES AND ENDPOINTS

The primary effectiveness objective of this study is demonstrating that treatment with favipiravir for COVID-19 patients with mild to moderate symptoms will shorten the time to sustained clinical recovery from study day 1 onward ('clinical endpoint component') compared to placebo.

The primary virologic objective (the secondary objective of the study) of the viral shedding sub-study is to demonstrate that treatment with favipiravir treatment will shorten the period of viral shedding ('viral shedding component') compared to placebo from study day 1 onward.

Demonstrate that treatment with favipiravir will reduce the proportion of subjects with COVID-19 related hospitalizations or emergency department visits compared to placebo from study day 1 onward.

Demonstrate that treatment with favipiravir will reduce the proportion of subjects with COVID-19 related hospitalizations or emergency department visits or the development from study day 1 onward of two or more new COVID-19 related symptoms compared to placebo from study day 1 onward.

Primary Efficacy Endpoint:

Time to Sustained Clinical Recovery defined as number of days from start of study treatment to Sustained Alleviation of Symptoms. The endpoint will be considered to have been met at the earliest time point from study day 1 onward at which the subject has reached Sustained Alleviation of Symptoms as defined by:

(1) Blood oxygen saturation $\geq$94% on room air at rest

(2) Oral temperature <38.0 ºC AND

(3) All COVID-19 associated symptoms (stuffy or runny nose, feeling hot or feverish, chills or shivering, cough, sore throat, lack of energy or tiredness, nausea, headache, muscle or body aches, shortness of

breath, vomiting, diarrhea) (Symptoms related to smell or taste are not included in the primary endpoint) reported by the patient have reached a severity of "0 – none" or "1 – mild" in assessments for 4-point scale assessments

To meet the primary endpoint, criteria 1 through 3 (above) should be met and the subject is not known to have redeveloped any COVID-19 associated signs and symptoms (not including reduced sense of taste or smell) at a severity beyond mild for 4 consecutive days (inclusive of the day when clinical recovery was achieved) assessed from the start of study treatment to day 28, and subjects must survive with no hospitalization to day 28. The time from start of study treatment to the earliest time point that one through three (above) are met will be considered for the primary efficacy endpoint. For example, if clinical recovery was reached on study day 5 and sustained over study days 6, 7, and 8, the time of reaching the endpoint will be study day 5.

The subject will assess and score the severity of each COVID-19 associated symptom on a 4-point scale (for all symptoms besides vomiting and diarrhea: 0= none, 1= mild, 2=moderate, 3=severe. For vomiting and diarrhea: 0 = not at all, 1 = 1-2 times, 2 = 3-4 times, 3 = 5 or more times). The patient's blood oxygen saturation and severity of COVID-19 associated symptoms will be evaluated and reported once daily, preferably at or around the same clock time, by the subject (for a period of 10 days or longer in case that the subject does not achieve the primary endpoint within the first 10 days).

Beyond Study Day 10, once the subject meets the primary efficacy endpoint, the subject is not required to continue the self-assessment and reporting of COVID-19 symptoms. However, the study team, during all the in-person and remote patient visits will evaluate and report the severity of each of the COVID-19 associated symptoms and vitals as per the set frequency mentioned in the *Schedule of Activities,* under study staff responsibility.

Subjects who develop new COVID-19 symptoms post-randomization will be counted towards the primary outcome. The definition of the primary endpoint for such subjects will be identical to the definition used for any other subjects. To have the endpoint, all symptoms (those existing at enrollment and those appearing post-enrollment, not including symptoms related to smell or taste) will have to be no worse than 1 - mild, regardless of whether they existed at randomization or not.

For any subject who has incompletely submitted relevant data to assess clinical recovery, the primary endpoint is met on the first day from study day 1 onward where clinical recovery is reached, defined as none of the symptoms is worse than mild, as well as temperature <38.0C and O2 saturation ≥94%, and considered sustained over the 3 following days when there is no known flare up of symptoms beyond mild. During the 3-day sustainability period, complete COVID symptom data (not including taste, smell) is required for at least 2 of the 3 days (COVID-19 symptom data can be missing for 1 of the first two sustainability days but not for the last day of sustainability). Missing information for temperature or O2 saturation during the 3-day sustainability period will not invalidate reaching the endpoint.

For any subject who has been lost to follow-up prior to Day 28, the investigators will make reasonable efforts to determine whether the subject has been admitted to the hospital or died up to Day 28. For subjects who experienced sustained clinical recovery prior to Day 28 and lost to follow-up, should the investigator be able to confirm no admission to the hospital and no death, the subject will be flagged as having the endpoint of sustained clinical recovery. Subjects who were lost to follow-up and for whom the investigator could not confirm lack of admission to the hospital or death before Day 28, will be flagged as the worst possible outcome regardless of clinical recovery.

Secondary Endpoints:

Key Secondary Efficacy Endpoint:

- Proportion of subjects with COVID-19 progression, where progression is defined as the occurrence from study day 1 onward of any emergency department (ED) visit for COVID-19 worsening or shortness of breath **OR** hospitalization for COVID-19 worsening or shortness of breath **OR** death (narrow progression)
- Proportion of subjects with COVID-19 progression, defined as the occurrence from study day 1 onward of any ED visit for COVID worsening or shortness of breath OR hospitalization for COVID worsening or shortness of breath OR death OR the development of symptomatic worsening from study day 1 onward (defined as ≥2 additional COVID symptoms at a level of moderate or severe which have not existed at baseline or fever (temperature of ≥38.0ºC) which has not existed at baseline or oxygen desaturation (O2 saturation <94%) which has not existed at baseline) (broad progression).

Viral Shedding Sub-Study:

- Time (number of days) to negative conversion (defined as undetectable viral load) of detectable SARS-CoV-2 viral RNA in RT-PCR assays of saliva, from start of study treatment to date of last viral assessment. Included: all subjects with a positive PCR on study day 1 or 2 or 3. The endpoint will be evaluated from study day 1 onward.

Additional Secondary Efficacy Endpoints

- Time (number of days) to negative conversion of positive SARS-CoV-2 viral culture assays of saliva, from start of study treatment to date of last viral assessment. Subjects with a positive saliva SARS-CoV-2 PCR on any study day will have viral cultures performed. Subjects with a positive viral culture on study day 1 or 2 or 3 will be included in this analysis. The endpoint will be evaluated from study day 1 onward.

Exploratory Endpoints (details of the planned analyses are described in SAP 3.1):

- Proportion of subjects showing sustained clinical recovery by study Day 1, 3, 5, 7, 10, 14, 21.
- Proportion of subjects showing resolution of Symptoms by Days 1, 3, 5, 7, 10, 14, 21, where resolution is defined as symptom severity of 0 for all symptoms as well as temperature of <38.0 ºC as well as oxygen saturation of ≥94%.
- Proportion of patients showing negative conversion of detectable SARS-CoV-2 viral RNA in saliva on study day 1 or 2 or 3 to undetectable viral load on Study Days 3, 5, 7, and 10. Included: all subjects with a positive PCR on study day 1 or 2 or 3.
- Proportion of patients showing negative conversion of positive SARS-CoV-2 viral culture in saliva on Study Days 3, 5, 7 and 10. Subjects with a positive saliva SARS-CoV-2 PCR on any study day

will have viral cultures performed. Subjects with a positive viral culture on day 1 or 2 or 3 will be included in this analysis.

- Proportion of subjects dying from any cause over an assessment period from start of study treatment until Day 28.
- Proportion of subject with COVID-19 progression, where progression is defined as the occurrence at any point from study day 1 to study day 28 of emergency department (ED) visit for any reason OR hospitalization for any reason.
- Proportion of subjects requiring mechanical ventilation over an assessment period from start of study treatment until Day 28.
- Time (number of days) to negative conversion (defined as viral load <100 copies) of detectable SARS-CoV-2 viral RNA (defined as viral load >100 copies) in RT-PCR assays of saliva, from start of study treatment to date of last viral assessment. Included: all subjects with a positive PCR on study day 1 or 2 or 3. The endpoint will be assessed from study day 3 onward.
- Time to Sustained Clinical Recovery defined as number of days from start of study treatment to Sustained Alleviation of Symptoms, evaluated from study day 3 onward.
- Proportion of subjects with COVID-19 progression, where progression is defined as the occurrence from study day 3 onward of any emergency department (ED) visit for COVID-19 worsening or shortness of breath OR hospitalization for COVID-19 worsening or shortness of breath OR death (narrow progression)
- Proportion of subjects with COVID-19 progression, defined as the occurrence from study day 3 onward of any ED visit for COVID worsening or shortness of breath OR hospitalization for COVID worsening or shortness of breath OR death OR the development of symptomatic worsening from study day 3 onward (defined as >2 additional COVID symptoms at a level of moderate or severe which have not existed (at any level of severity) at baseline or fever (temperature of ≥38.0ºC) which has not existed at baseline or oxygen desaturation (O2 saturation <94%) which has not existed at baseline) (Broad progression).

Safety Endpoint:

1. Number (and proportion) of patients reporting treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term). See additional information on assessing adverse events under section 9.4.
2. Number (and proportion) of patients reporting serious treatment emergent adverse events (TEAEs) (by MedDRA system organ class and preferred term).
3. Vital Signs including oral temperature, heart rate, oxygen saturation with height and weight.
4. Clinical laboratory tests including Biomarkers, Chemistry, Coagulation and Hematology.

5.0 STUDY DESIGN

5.1 Overall Design

This is a double-blinded, randomized, placebo-controlled, superiority trial of approximately1250 adult outpatients with mild to moderate symptoms of COVID-19 not requiring hospitalization. Depending on the site of enrollment, subjects will be identified at COVID-19 testing centers, testing laboratories, or other clinical care settings. As this study will enroll outpatients only, to prevent violating quarantine requirements and decrease risk of COVID-19 for study team members, most study interactions will be performed remotely with no need for study subjects to leave their homes to fulfill their study obligations. Besides study visits on Day 1 and Day 10, which will be in-person, all other study interactions will be done remotely, using telehealth and video conferencing. Study materials will be provided to subjects at their home or in-site.

Subjects in the treatment arm (n= 625) will receive favipiravir orally taken approximately every 12 hours in addition to current standard of care treatment. The first two doses of favipiravir will be 1800 milligrams. The following doses will be 800 milligrams for a total of 10 days of therapy. Those in the control group (n= 625) will receive placebo orally, using the same numbers of tablets on day 1 and the subsequent 9 more days (total 10 days of treatment), in addition to current standard of care treatment. Saliva PCR testing will be performed at an accredited central laboratory. The site's Principal Investigators will be responsible for study recruitment and engaged as deemed necessary by the Study Team to ensure identification and reporting of maximum number of positive cases and prompt subject engagement/ enrollment. This study will be listed at www.clinicaltrials.gov.

Subjects who provide informed consent, meet all inclusion and no exclusion criteria will be randomized on Treatment Day 1 in a 1:1 ratio to either the Treatment Group or the Control Group, in accordance with a computer-generated schedule prepared by a biostatistician. The randomization schedule will be incorporated into the Interactive Web Randomization System (IWRS). Randomization will then be performed by study personnel directly in the IWRS system. Study personnel will be instructed not to randomize until subject has been confirmed to meet all inclusion/exclusion criteria on treatment Day 1.

5.2 Scientific Rationale for Study Design

Randomized, double blind, placebo control (RDBPC) studies provide the strongest possible evidence of causation. Phase III trials are used to expand on Phase II research of the efficacy and safety of an intervention in subjects with the disease for which a new intervention is proposed. Randomization in combination with blinding helps to avoid possible bias in the selection of subjects, their assignment to an intervention or control, and the analysis of their response to the intervention.

5.3 Dose Justification and Tablets needed

5.3.1 Justification for Dose

Favipiravir will be taken approximately every 12 hours. The dosage for favipiravir to be used in this study is 1800 mg (9 tablets of 200 mg) orally for the first 2 doses, then 800 mg orally approximately every 12 hours to complete days 2-10 of therapy. 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. Although discouraged, if necessary, favipiravir may be crushed for administration and can be

taken with or without food [24-25]. This dosing strategy is increased from the licensed dosing regimen for influenza, to account for the higher in-vitro concentrations required for activity against SARS-CoV-2. Elevated dosing strategies, up to 6000 mg on day 1 followed by 1200 mg BID has been used in published Favipiravir studies for Ebola [26]. Prolonged administration to 22 days has been explored in a phase 1 study in Japan (JP120) with a favorable safety profile (patients received 1800 mg PO BID on day 1 followed by 800 mg PO BID from day 2-21 and a single dose of 800 mg on day 22).

5.3.2 Number of tablets required for the entire study

For a 10-day course: 1800 mg (9 tablets of 200 mg) x2 doses (a total of 18 tablets), then 800 mg (4 tablets) x2 daily doses until study day 10 (8 tablets per day to complete 10 days of therapy) for a total of 90 tablets per subject for the entire study period. Tablets required for dosing of the entire study population per treatment arm will be 56,250 (625 subjects x 90 tablets per subject).

Considering competitive enrollment involving multiple countries and sites, it is very critical to maintain sufficient quantity of IPs at each IP depot and participating sites. Hence, it would require to add-on approximately 50% contingency quantity. This will make up to total approximately 85,000 tablets for the entire study per each treatment arm.

5.4 Dosing in Special Populations

Favipiravir is contraindicated in nursing mothers and pregnant women or women of child-bearing age who are not taking oral contraception due to its potential teratogenicity. No alteration of dosing is needed in subjects with renal impairment. Total exposure for plasma favipiravir for subjects with severe renal impairment (Stage 4) was 1.3-fold higher compared to subjects with normal renal function. No obvious effect of renal impairment on safety was observed and favipiravir treatment was generally well tolerated in subjects with renal impairment.

No alterations in dosing strategies are required in older adults. The maximum plasma concentration and AUC values in elderly subjects in a single and a multiple-dose study completed in Japan were higher than in young subjects. Comparing AUC values on Day 5, the differences were 40 and 80% after 600 mg once a day and 400 mg BID, respectively. In the companion study completed in the United States of America, there were no differences between young and older populations based on Day 5 AUC comparison in subjects receiving either 600 or 800 mg BID.

5.5 Storage and Stability

Favipiravir is a novel nucleic acid (pyrazine molecule) analogue that interferes with viral ribonucleic acid (RNA) replication. Favipiravir is supplied as a light yellow, film-coated tablet for oral administration containing 200 mg favipiravir. Favipiravir tablets are to be kept in a dry area, stored at 15° C to 30° C and shielded from direct light.

5.6 Study Drug Dispensation

Study drug will be provided from IP depot to the research site. The research site study team member will distribute the IP to each enrolled subject. If transportation is needed, the research site study team member will be responsible for transporting of medications to each enrolled subject.

5.7 Expected Side Effects

Favipiravir is considered a safe drug. No treatment related serious adverse events occurred in licensure studies of favipiravir [2]. The most common adverse events observed in clinical trials are gastrointestinal (diarrhea 2.3%; nausea 2.1%). A similar proportion of subjects in the placebo (25.4%) and favipiravir (25.3%) groups experienced at least 1 adverse event. Further, favipiravir is associated with increased uric acid level which are typically asymptomatic and would be expected to be transient with the duration of treatment to be used in this trial.

5.8 Additional Safety Considerations

For the purpose of this trial, the following are exclusion criteria for study drug administration:

1) Subject has a history of hypersensitivity to favipiravir

2) Known uncompensated hepatic cirrhosis.

3) Current use of the following medications, which cannot be discontinued for the duration of the study: pyrazinamide, hydralazine, more than 3000 mg of acetaminophen per day.

The following safety considerations are based on data from individuals taking favipiravir for influenza. They are listed here for reference.

- Phototoxicity: Nonclinical studies have shown mild phototoxicity. One study subject experienced mild photosensitivity (rash) following a tanning bed session. All subjects should avoid excessive exposure to sunlight or artificial ultraviolet light.
- Laboratory Values: Mild to moderate asymptomatic elevations of uric acid and aminotransferase have been observed in healthy volunteers and subjects with influenza [2] treated with favipiravir in clinical studies. The changes have been reversible upon favipiravir discontinuation.
- Mutagenesis: Favipiravir proved mildly positive under some conditions studied in the mammalian chromosomal aberration test and mouse lymphoma assays at high concentrations. Although the potential for genotoxicity at high exposures cannot be ruled out, evidence indicates that this risk is minimal at the exposures planned in this clinical study.
- GI Tract Lesions: In two proof-of-concept studies of orally administered favipiravir against Ebola virus infection in macaques, GI tract lesions were observed that were not consistent with the known natural history of Ebola nor with previous animal and clinical studies of favipiravir. However, evidence suggests that bacterial infections and pre-existing enterocolitis in the treated macaques may have been responsible, and an ongoing risk to subjects may not exist.
- Contraception:

Females of Childbearing Potential

Female subjects who are of childbearing potential must use an acceptable method of contraception starting from screening through to at least 7 days following the last dose of study medication. Acceptable contraceptive methods for female subjects of childbearing potential include one of the following:

1. Abstinence.
2. One of the following methods:
   - Tubal ligation 4 or more weeks prior to randomization
   - Copper-containing intrauterine device (IUD).
   - Condom AND spermicidal foam/gel/film/cream/suppository.
   - Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected.
   - Hormonal contraceptives (oral, injected, transdermal or implanted). The subject must remain on the treatment throughout the study and must have been using hormonal contraceptives for an adequate period to ensure effectiveness (3 months prior to randomization or longer).

Females of Non-Childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal females (Not menstruating for at least one year)
2. Females who have a documented hysterectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

Men

Men must meet at least one of the following criteria:

1. Known to be sterile (have azoospermia)
2. Underwent vasectomy
3. Use condom

5.9 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the section of *Schedule of Activities*, or is hospitalized or dies before the 28 day follow-up visit.

5.9.1 Early Termination/Hospitalization

All subjects have the right to withdraw from study participation at any time during the study. If, for whatever reason, a subject withdraws from the study or is hospitalized for increased severity of COVID-19 symptoms or other cause, an **Early Termination Visit** will be performed as deemed feasible by the PI or qualified designee.

Any AE, SAE or other medical condition or situation that occurs such that continued participation in the study would not be in the best interest of the subject will result in early termination.

The following procedures will be performed at the ***Early Termination Visit*:**

1. Assess for AEs
2. Document all current medications, including medications over the counter and herbal medications
3. Perform clinical assessment (as deemed feasible if hospitalized)
4. Evaluate for increased severity of COVID-19 related disease and symptoms
5. Pregnancy Test for women of child-bearing potential

If clinical evaluation is deemed not feasible due to subject's condition, the study team will collect as much of the Early Termination Visit data and attempt to complete Day 21 and Day 28 assessments and AE assessment for those who are hospitalized and deemed off study.

6.0 STUDY POPULATION

6.1 Inclusion Criteria

The study will include subjects with mild-to-moderate COVID-19.[33] Study subjects should meet all of the following criteria:

1. Adults age 18 or older
2. Tested positive for SARS-CoV-2 by RT-PCR or Rapid Antigen assay (first positive test) using a respiratory tract sample (either nasopharyngeal swab OR oropharyngeal swab OR nasal aspirate OR tracheobronchial aspirate OR saliva) collected within 72 hours of randomization
3. Stated willingness to give their written informed consent to participate in the study
4. Stated willingness to comply with all study procedures and availability for the duration of the study
5. Males must be sterile, OR agree not to donate semen AND agree to strictly adhere to contraceptive measures (e.g. condom use) during the study and for 7 days following the last dose of study medication
6. Females must be unable to bear children, OR ensure that their male partner is incapable of fathering a child, OR, if of childbearing potential will strictly adhere to contraceptive measures during the study and for seven days following the last dose of study medication (as detailed in section 5.8)
7. Females must agree to stop breast-feeding prior to first dose of study drug and through seven days after completing therapy
8. Females must have a negative pregnancy test at screening
9. Ability to take oral medication and be willing to adhere to the favipiravir/placebo regimen

10. Minimal baseline severity score for COVID-19-related symptoms: at least two symptoms with a score of 2 or higher. COVID-19-related symptoms include: Stuffy or runny nose, sore throat, shortness of breath, cough, lack of energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, diarrhea, vomiting. (Excluding changes in the sense of taste or smell).

11. Subject has access to a smart phone, tablet, or PC

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. O_2 saturation <94%
2. Shortness of breath at rest
3. Heart rate ≥ 125 per minute
4. COVID-19 symptoms first presented >5 days prior to randomization
5. Requirement for hospitalization at the time of enrollment
6. Participation in another trial or use of any experimental treatment for COVID-19
7. Treatment with high steroid dose i.e. >30 mg/day prednisolone equivalent (excluding stable chronic treatment) or remdesivir or anyone receiving SARS-CoV-2 monoclonal antibodies within 3 months prior to enrollment
8. Known sepsis or organ dysfunction/ failure
9. Known infection with a respiratory virus other than SARS-CoV2 (e.g. Influenza) or any known bacterial infection (affecting the respiratory system or any other system)
10. Inability to adhere to study requirements
11. For premenopausal women: unwilling or unable to use effective birth control measures
12. Known allergy to favipiravir
13. Known end-stage kidney disease or requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD)
14. Known liver impairment greater than Child-Pugh A
15. Psychiatric illness that is not well controlled (defined as stable on a regimen for more than one year).

16. Known elevated uric acid levels in the past year or taking uric acid lowering medications (allopurinol, febuxostat)

17. History of hereditary xanthinuria or history of xanthine urolithiasis.

18. History of gout or actively being treated for gout.

19. Current use of the following medications, which cannot be discontinued for the duration of the study: pyrazinamide, hydralazine, more than 3000 mg of acetaminophen per day.

6.3 Lifestyle Considerations

No special preparations or additional steps (for example, special diets, fasting, other medicines, laxatives, or enemas) are necessary before, during, or immediately after taking favipiravir. For reasons unrelated to study participation, the standard of infection prevention in communities is the quarantine of individuals who test positive for COVID-19. This standard is expected to continue and be practiced throughout the study period in all countries and states where the study will be enrolling.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6.5 Strategies for Recruitment and Retention

The strategy for recruitment will depend on the site of recruitment. Subjects will be identified at COVID-19 testing centers at the occasion of testing, through COVID-19 testing laboratories upon receipt of testing results, or at other clinical care settings. When identified at testing centers, tested individuals will be asked for their permission to be approached after testing to inquire about their interest to participate in the study. HIPAA-governed procedures related to subject enrollment into this study will be practiced in a HIPPA-compliant manner or *Lei Geral de Proteção de Dados Pessoais (LGPD)* in Brazil. This will include:

1) Obtaining IRB approval to approaching persons who may test or have tested positive for SARS-CoV2
2) Testing centers, testing labs, and care organizations that are involved in the study and whose clinical role is to report SARS-CoV2 test results, will read a statement to patients who tested positive to get their verbal permission to be called by the study team about the study
3) The statement will be as followed: “You may test/have tested positive for COVID-19 and may be eligible to participate in an Appili Therapeutics research study from the comfort of your home. We are asking for your permission to provide your contact information to the clinical research team who will contact you to see if you are interested in participating. If you’d like to reach out to the research team yourself, the direct number is XXX-XXX-XXXX"

4) Those who provided a verbal permission to be approached after testing, will be called by the study team.
5) Individuals who express interest to participate in the study will be screened for inclusion and exclusion criteria. If they qualify, they will be educated about the study medications and the study procedures. If they consent to participate, they will be randomized into the study.
6) If required, social media may be used to enhance recruitment.

7.0 STUDY INTERVENTIONS

7.1 Study Intervention(s) Administration

7.1.1 Study Supplies

On study day 1, after randomization, study subject will be supplied the study kit. The study kit will include the following:

1. Thermometer with the specific instructions how to measure and document temperature
2. Fingertip probe pulse oximeter, with specific instructions how to measure and document oxygen saturation and heart rate. The relatively low reported percentage of error for the finger probe supports that the finger probe is the modality of choice to measure intermittent oxygen saturation in the outpatient setting.
3. Sterile saliva collection tubes
4. IP kit (Favipiravir or placebo tablets).
5. For premenopausal (child bearing potential) women: Urine pregnancy test. To be performed on Day 1, Day 7, and Day 28 (or earlier in the case of early study termination).
6. On randomization (Study Day 1), subjects will be educated and trained on the use of the thermometer, pulse oximeter, pregnancy test.

7.1.2 Study Vital Signs Measurements and Health Information

- Oral Temperature: will be measured 2 times daily. It will be documented in the subjects' diary. Subjects will be allowed to take temperature lowering medications such as acetaminophen or NSAIDS.
- Heart rate: will be measured once daily and documented by the subject in the subject's diary.
- Oxygen Saturation: will be measured once daily and documented by the subject in the subject's diary. If the O_2 saturation result is 90-93%, the subject will repeat the measurement 2 hours later. If the result is <90%, the subject is instructed to contact the study team. The study team will decide if a recheck in 2 hours is appropriate or the subject needs further medical evaluation).
- Height and weight: Height and weight should be collected at the screening visit. In cases where this has not occurred at the screening visit, the date of collection will be recorded.

7.1.3 Dosing and Administration

Subjects will be randomly assigned to favipiravir (the first two doses are 1800mg given approximately 12 hours apart and followed by 800mg approximately every 12 hours to treatment day 10) or identically dosed placebo in 200 mg tablets. All tablets will be supplied in a bottle.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Acquisition and accountability

In accordance with recent COVID-19 FDA Guidance, if scheduled visits at clinical sites are significantly impacted, certain IP, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods, via a courier.

Favipiravir and matching placebo (Investigational Product, IP) will be stored in central IP depot and research site. Upon enrollment, the research site will dispense the IP to the subject. The entire supply of study medication will be dispensed at one time. Subjects will be asked to document compliance with study protocol in a subject diary. If a subject does not use all the IP, the remainder shall be returned to the study site by day 28. Returned IP and unused IP that has never been delivered to subjects will be returned to the IP depot with prior approval of CRO/ Sponsor.

The study medication will be packed in individual subject's kits, labeled with study specific labels, and supplied to the study sites. Labels will reflect appropriate dosing and storage information, the use for the investigational purpose only, plus a unique number that will be used to assign the medication to the subject according to their randomized treatment assignment (IWRS).

7.2.2 Formulation, Appearance, Packaging, and Labeling

Table 1. Formulation, Appearance and Composition of Favipiravir®	
Formulation	$C_5H_4FN_3O_2$; favipiravir
Appearance	Light yellow to yellow, film-coated, round tablets, plain on both sides
Packaging	HDPE Bottles with induction seal and child resistant cap.
Sample Label	CFR 21 Part 312 Sec. 312.6 Labeling of an investigational new drug.: Protocol#: ATI0220 Product Name: Favipiravir/ Placebo Strength/Formulation: 200mg/Tablet Quantity per container: Lot/batch number: Expiration/retest date: Medication number (Kit no.):

	Storage requirements: 15-30°C Investigator: Subject number: Name and address of sponsor: Appili Therapeutics Inc., 21-1344 Summer Street, Halifax, Nova Scotia, B3H 0A8, Canada Emergency Contact: Keep away from Children Caution: New Drug- -Limited by Federal law to investigational use.

7.2.3 Product Storage and Stability

Favipiravir and the matching placebo are oral tablets. They can be stored at room temperature, 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). Short-term excursions to higher temperatures during shipping and handling, e.g. to 40 °C, do not affect the quality of the material as a satisfactory stability was also shown under these conditions.

7.2.4 Preparation

There will be no significant preparation. Tablets will be dispensed in a white HDPE Bottle with induction seal and child resistant cap in accordance with state and federal regulation. Favipiravir may be crushed for administration and can be taken with or without food [24-25].

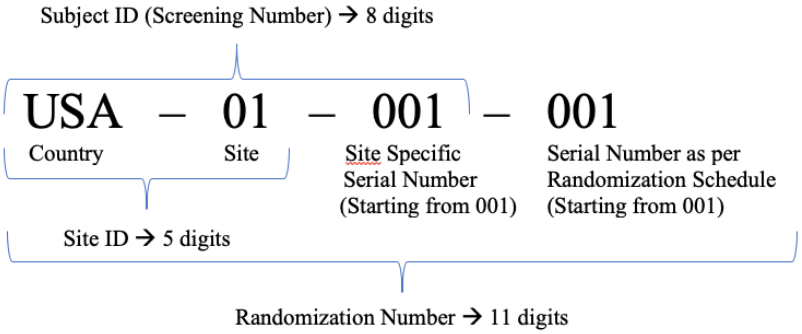
7.3 Measures to Minimize Bias: Randomization and Blinding

Subjects who sign informed consent and meet all inclusion and none of exclusion criteria will be randomized on Day 1 in a 1:1 ratio to either the Test (Favipiravir) or Placebo, in accordance with a computer-generated schedule prepared by a biostatistician. The randomization schedule will be incorporated into the IWRS. Randomization will then be performed by study personnel directly in the IWRS. Study personnel will be instructed not to randomize until subject has been confirmed to meet all eligibility criteria of the study.

As all members of the study team will be blinded, Investigational Drug Services (IDS) and/ or IP depot will be unblinded and will dispense both the favipiravir and placebo, as needed. The study intervention (favipiravir) and placebo will be packaged as indistinguishable as possible.

Assignment of Subject Identification (Screening number), Randomization number and study medication, as well as site drug inventory control and emergency subject unblinding, will be managed by an automated Interactive Web system (IWRS). A manual containing complete instructions for web access and use will be provided to each site prior to study start. During screening, the IWRS will assign a Screening Number (Subject ID number). Each Subject ID number will be unique and serve as the primary subject identifier throughout the study. The subject ID number must appear on all CRF pages, source documents and lab data. Subjects qualifying to enter the double-blind treatment phase, will be assigned an additional Randomization Number by the IWRS at baseline visit on day 1, before the drug is dispensed.

Example of Site ID, Subject ID and Randomization Number*:



* Other numbering pattern can be adopted and defined in separate plan/ manual.

Refer to ***Section of Statistical Considerations*** for sample size calculations.

7.4 Study Intervention Compliance

During the Baseline and Screening (Day 1), the Principal Investigator (PI) or qualified designee will review the study with the subject and obtain informed consent and follow *Lei Geral de Proteção de Dados Pessoais (LGPD)* in Brazil or Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization, where applicable. A second member of study team (e.g., the study Clinical Research Coordinator (CRC)) will serve as a witness to the informed consent. After the informed consent is obtained, the subject will be assigned a unique enrollment number. The subject will then be randomized to treatment in IWRS and provided blinded treatment (either Favipiravir or placebo) and other study materials.

On Treatment Day 1, a member of the study team or study CRC will review the dosing and schedule of favipiravir/ placebo with the subject.

- The subject will be instructed to record all doses in Study Drug Administration Diary
- During each remote patient visit, the study CRC or other Study Team member will review the diary with the subject
- The subject will be advised not to discard any study tablet(s)

Refer to the Section of Schedule of Activities.

7.5 Concomitant Therapy

Concomitant therapies are any new or existing medications or therapy taken by the subject including:

Drugs, including but not limited to, prescription, over the counter, birth control tablets/patches/hormonal devices, and homeopathic preparations.

- Nondrug therapies, including but not limited to, thermal/laser/radiation procedures, vitamins, herbal medicines/supplements.

During the screening process, information on all concomitant therapies, medications, and procedures will be recorded in the source documents and appropriate Case Report Form (CRF) along with the diagnosis or reason for use. Once the subject receives the first dose of study drug, recording of concomitant therapies will be limited to any new medication or modification of an existing medication taken for treatment of an AE. These therapies will be recorded in the source documents and appropriate CRF along with the diagnosis or reason for use. Those therapies used for the treatment of an adverse event are to be linked to an AE and documentation of the AE must also be completed

7.5.1 Rescue Medicine

The study site will not supply rescue medication.

7.6 Telemedicine

The sites will use their existing remote patient visit (e.g. telehealth) platform in accordance with any local, state or country regulations. (E.g. AM Well, Doximity, or other).

Subjects must have access to a smart phone, tablet or PC to participate in the study. Subjects will be guided through the step-by-step setup on their smart phone by the study CRC. Guidance will be provided to the study CRCs to ensure that instructions provided to subjects are consistent. For example, the study CRC will provide instruction in simple, easy to understand language such as, *"I am going to take a minute and walk you through signing up for the app so you are ready on your visit date". "I've have actually gone ahead and scheduled the visit for you in the app". "The app is navy blue, has a picture of a doctor with a stethoscope and lighter blue heart".* Once set up, a reminder of the upcoming appointment will be sent to the subject via email, text message, or phone call.

7.7 Viral Shedding Testing

7.7.1 General Description of the Testing Process

The specimen to be tested for SARS-CoV2 RNA and viral cultures is saliva. The choice of saliva as the specimen stems from the need to minimize risk and discomfort to subjects as they will be having the test on 10 consecutive days. Both nasopharyngeal and mid-turbinated specimens require a semi-invasive collection procedure, which is less safe, less feasible, and associated with discomfort. The saliva specimen will be collected by the subject at their residences. Education and training on specimen collection will be provided in the clinic by a study team member on Day 1. The specimen will be transferred to the study's central laboratory in two occasions during the first 10 days of the study (Study Days 5+1 and 10+1). An approved PCR-based test will be performed by the accredited study's central laboratory. Viral cultures will be performed for subjects whose day 1 or 2 or 3 saliva specimen is PCR positive.

7.7.2 Specimen Collection Kit

On Study Day 1, the subject will be supplied the study kit. It will include 11 (1 extra) sterile saliva plastic collection containers of 10 mL each labeled as 'Study Day 1', 'Study Day 2' and so on.

7.7.3 Specimen Collection Days

Saliva Specimens will be collected by the subject at Study Days 1 to 10. Care will be taken to ensure that sampling methods are consistent for each individual subject across all included timepoints, to limit any

bias due to potential differences in viral load. The first collection of saliva samples will be observed by a Study Team member during Day 1 in-person visit.

7.7.4 Specimen Collection Procedure

Saliva collection, storage, and shipment procedure:

Subjects will be trained by a study team member of the technique of saliva collection. Saliva collection will be observed by the study team member.

1) Saliva will be collected into an empty sterile mL-marked tube (lacking preservatives or buffers).
2) The subject will wash hands before opening the test package.
3) Within 30 minutes of the saliva collection, the subject will avoid eating, drinking, smoking, chewing gum, or brushing their teeth.
4) The subject will spit their saliva into the tube until the saliva reaches the black line on the tube (2 ml).
5) The subject will remove funnel and screw on cap to release blue preservation agent into the tube.
6) The subject will place the specimen in the provided biohazard bag. Seal the biohazard bag by closing the zip lock seal. Wipe the bag with the provided alcohol wipe. Wash hands thoroughly again.
7) The subject will keep the tube at room temperature.
8) Saliva tubes collected on study days 1-5 (4 x 24-hour periods are required to complete their collection) will be shipped on study day 5 (+1) from the subject's home to the central laboratory.
9) Saliva tubes collected on study days 6-10 will be collected by a study team member on study day 10 (+1) and shipped to the central laboratory.
10) Specimens will be processed and tested immediately after their arrival at the central laboratory.

7.7.5 Specimen storage until shipping to laboratory

The saliva specimen remains stable for at least 10 days in room temperature. It will be stored at the subject's residence at the collection container in room temperature.

7.7.6 Specimen Shipping

The saliva specimens will be shipped to the testing laboratory in two batches: on Study Day 5+1 and Study Day 10+1. The specimens will be shipped in room temperature.

7.7.7 Specimen Testing

The specimens will be tested to identify RNA copies of SARS-CoV2 by means of a semi-quantitative RT-PCR technique using FDA approved 'Saliva Direct' testing protocol.[34] For quantitation of RNA in the specimen- as there is no FDA-approved quantitative RT-PCR for SARS-CoV2, we will be using the following methodology:

1) The PCR CT counts will be documented for each specimen,
2) To estimate RNA viral loads from CT counts, external controls with known RNA load will be used,
3) The controls will be PCR tested and their CT count will be correlated to their know RNA load,

4) These data will be used to create a validated curve associating CT counts to RNA load,
5) The curve will be used to estimate RNA loads in specimens from trial subjects.

The sensitivity and specificity of FDA approved 'Saliva Direct' testing protocol when comparing saliva to the gold standard specimen of nasopharyngeal swab are 94.1% and 90.9%.[34] As for the stability of SARS-CoV2 RNA in saliva specimens lacking preservative or buffer and kept in room temperature- initial studies demonstrated adequate stability for at least 5 days (as an example- the Advanta Dx SARS-CoV-2 RT-PCR Assay, which has an EUA approval by FDA).[35] Additional studies demonstrated adequate stability up to 21 days (pre-published data).[35]

Saliva specimens from subjects tested positive by PCR on any study day will be processed for SARS-CoV-2 viral cultures. Culture positivity will be determined by screens for SARS-CoV-2 induced cytopathic effect of Vero E6 TMPRSS2 cells after 3 days of incubation. The screen is appropriate for nasal or saliva samples from patients that are known to have the SARS-CoV-2 virus infection by PCR.

In addition, testing will be performed to evaluate the possibility of viral resistance and to identify SARS-CoV-2 variants (including but not limited to variants B.1.526, B.1.525, B.1.617, P.2, B.1.1.7, B.1.351, P.1, B.1.427, B.1.429, as well as other dominant variants that emerge during the pandemic). The identification of favipiravir variants, as well as favipiravir mutations that could confer favipiravir drug resistance will be performed using whole genome sequencing. Attempts will be made to compare paired specimens (i.e., from the same subject) collected before or early during the favipiravir dosing period and specimens collected at or near the end of the favipiravir dosing period.

8.0 STUDY INTERVENTION DISCONTINUATION AND SUBJECT WITHDRAWAL/ DISCONTINUATION

8.1 Discontinuation of Study Intervention

This study may be temporarily suspended or prematurely terminated if there is enough reasonable cause. If the study is prematurely terminated or suspended, the study team will promptly inform the Study Review Board and will provide the reason(s) for the termination or suspension.

Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by early termination procedures in Section 8.2.3 of the study protocol. The possible reasons for early study discontinuation are listed in Section 8.2.2 and withdrawal procedure is described in Section 8.2.1. The subjects will be contacted by the study team remotely (for example, by using phone or telehealth application) to complete these procedures. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE. During the early termination visit upon withdrawal or discontinuation, the subject will be accessed for AEs, the use of any concomitant medications will be documented, a clinical assessment will be performed (if feasible and permitted), an assessment of COVID-19 symptoms will be conducted, a test for pregnancy in women of child-bearing potential will be completed, and any used-IP will be returned by the subject. All information will be documented in the CRF. If a study participant withdraws or is discontinued from the study, they will not be replaced.

8.2 Subject Discontinuation/Withdrawal from the Study

8.2.1 Study withdrawal procedure

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and the CRF. The study team will make every effort to contact subjects who are lost to follow-up. Attempts to contact such subjects will be documented in the subject's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, etc.).

8.2.2 Reasons for early study discontinuation

A subject may be discontinued from the study at any time if the subject, the study team or PI feels that it is not in the subject's best interest to continue. The following is a list of *possible* reasons for study discontinuation:

1) Subject decides to withdraw their consent
2) Occurrence of any SAE that the site investigator believes is or may be related to the study drug
3) Occurrence of 2 or more grade 4 or higher AE that the site investigator believes is or may be related to the study drug [CTCAE v-5 has 5 severity grades/ see attached]
4) Based upon the decision of the site PI: the occurrence of any medical condition or situation that is creating a situation in which continued study participation will not be in the subject's best interest
5) Any death of a subject that the site investigator believes is or may be related to the study drug
6) The subject is lost to follow-up
7) Subject hospitalization for any reason at any point during the 28 days of the study
8) The subject has become pregnant

8.2.3 Procedures to be performed at the Early Termination visit

- Assess for AEs
- Document all current medications, including medications over the counter and herbal medications
- Perform clinical assessment (as deemed feasible if hospitalized)
- Evaluate for increased severity of COVID-19 related disease and symptoms
- Pregnancy test for women of child-bearing potential

If clinical evaluation is deemed not feasible due to subject condition, the Study Team will collect as much Early Termination Visit data as possible from the Electronic Medical Record

The reason for subject discontinuation or withdrawal from the study will be recorded on the CRF.

8.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to complete more than (2) scheduled remote patient visits and is unable to be contacted by the study staff.

The following actions must be taken if a subject fails to appear for a required telemedicine study visit:

1. The Study Team will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.

2. Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will be documented in the subject's medical record or study file.
3. Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

For subjects considered lost to follow-up, the CRF will be completed up to the last contact with the subject.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 Efficacy Assessments

The specific timing of procedures/evaluations to be done at each study visit are found in Section of "Schedule of Activities". All assessment will be performed by the study investigators and/ or a qualified member of the study team.

9.2 Study Procedures

9.2.1 Screening, Baseline, Randomization and Treatment (Day 1)

The following procedures will be performed at the Day 1 in-person visit:

- Confirmation of positive SARS-CoV-2 test result
- Confirm subject meets all inclusion and none of the exclusion criteria
- Review the study with the subject and obtain written informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization, or equivalent in another respective country, as applicable such as *Lei Geral de Proteção de Dados Pessoais (LGPD)* in Brazil
- Register the subject in IWRS to allot a unique subject ID (screening number)
- Randomize subject to treatment arm in IWRS as per randomization schedule
- IWRS to assign unique randomization number to the subject
- IWRS to assign IP kit number as per randomization schedule
- Record demographics (age, race, ethnicity, gender)
- Review and record medical history, surgical history
- Review and record smoking, alcohol and medication history
- Document all current medications, including medications over the counter and herbal medications
- Record height and weight
- Record COVID-19 symptoms for inclusion
- Record confirmation of positive SARS-CoV-2 test result
- Record number of days since onset of symptoms
- Collect blood sample for below listed blood tests:
    - CBC with differential, Electrolytes, BUN, Creatinine, Random Blood Serum Glucose, AST, ALT, Bilirubin, uric acid, SARS-CoV2 IgG, IL-6, IL-10, ESR, CRP, D-Dimer, ferritin. (CRP = C-reactive protein, IL-6 = Interleukin-6, IL-10 = Interleukin-10, CBC = Complete Blood Count).
    - Site do not require to wait for blood test result to randomize subjects.

- Provide the allotted IP kit, the blinded treatment (either favipiravir or placebo), and other study materials to the subject
- Assist the subject in downloading the ePRO app, create ePRO credentials for the subject, train the subject on how to use the ePRO and enter the Day 1 Dose 1 visit data with the subject during the visit to ensure the subject's understanding.
- Until the sub-study enrollment is completed (112 events have been counted), all subjects will be enrolled into the viral shedding sub-study. However, if they choose so, subjects can opt-out of participating in the viral shedding sub-study.

9.2.2 Treatment Day 1 to Day 10

- In-person clinical assessment will occur on study Day 1 as described in section 9.2.1 and on Day 10 as described in section 9.2.3. Remote patient visits will occur on study Day 3, 5, 7, and 9.
- Subjects to self-administer IP (Favipiravir/ Placebo) as per the instruction provided and report in diary twice daily. Site staff to assess IP adherence daily.
- Subjects to report Adverse Event and Concomitant Medications including OTC and herbal products daily.
- Site staff to assess Adverse Event and Concomitant Medications including OTC and herbal products daily
- Subject to collect oral temperature twice daily, and report in the diary.
- Subject to collect oximetry data once daily, with the caveat that if O_2 goes below 94%, an additional oximeter reading should be taken 2 hours later. If the daily O_2 saturation result is 90-93%, the subject will repeat the measurement 2 hours later. If the result is <90%, the subject is instructed to contact the study team. The study team will decide if a recheck in 2 hours is appropriate or the subject needs further medical evaluation)
- The patient's severity of COVID-19 associated symptoms will be evaluated and reported once daily, preferably at or around the same clock time, by the subject (for a period of 10 days or longer in case that the subject does not achieve the primary endpoint within the first 10 days). The study team will be reviewing the data reported by subject to ensure compliance, accuracy and completeness on days 1, 3, 5, 7, 9, 10, 14, 17, 21, 24, and 28.
- The subject will assess and score the severity of each COVID-19 associated symptom on a 4-point scale (for all symptoms besides vomiting and diarrhea: 0= none, 1= mild, 2=moderate, 3=severe. For vomiting and diarrhea: 0 = not at all, 1 = 1-2 times, 2 = 3-4 times, 3 = 5 or more times).
- Viral specimen (saliva) collection, storage and shipping (refer section 7.7 for more details).
- Refer "Schedule of Activities" table for additional information on activities and whether they are the responsibility of subjects and/or study team.

9.2.3 Treatment Day 10

In addition to procedures described in 9.2.2, the following procedures will be performed at the in-person follow-up visit on Day 10.

- Assess for AEs
- Review and assess COVID-19 signs and symptoms
- Document all current medications, including medications over the counter and herbal medications
- Document subject's status as an outpatient, subsequently hospitalized, or died

- Perform clinical assessment and review reported vital signs (oral temperature, heart rate and oxygen saturation)
- Collect blood sample for below listed blood tests:
    - CBC with differential, Electrolytes, BUN, Creatinine, Random Blood Serum Glucose, AST, ALT, Bilirubin, uric acid, SARS-CoV2 IgG, IL-6, IL-10, ESR, CRP, D-Dimer, ferritin. (CRP = C-reactive protein, IL-6 = Interleukin-6, IL-10 = Interleukin-10, CBC = Complete Blood Count).

9.2.4 Post Treatment Days (Day 14 to Day 28)

The following procedures will be performed at all follow-up visits (post-treatment days), expected to be done remotely, unless otherwise noted, on Day 14, 17, 21, 24, and 28:

- Assess for AEs
- Review and assess COVID-19 signs and symptoms
- Document all current medications, including medications over the counter and herbal medications
- Document subject's status as an outpatient, subsequently hospitalized, or died
- Perform clinical assessment and review reported vital signs (oral temperature, heart rate and oxygen saturation)
- The study team will be reviewing the data reported by subject to ensure compliance, accuracy and completeness on days 1, 3, 5, 7, 9, 10, 14, 17, 21, 24, and 28.
- Once the subject meets the primary efficacy endpoint, the subject is not required to continue the self-assessment and reporting of COVID-19 symptoms. However, the study team, during the remote patient visits will evaluate and report the severity of COVID-19 associated symptoms as per the set frequency mentioned in the *Schedule of Activities,* under study staff responsibility.

9.2.5 Final Study Visit (Non-hospitalized Subjects) (Day 28)

The following procedures will be performed at the final post treatment visit (remote patient visit):

- Assess for AEs
- Document all current medications, including medications over the counter and herbal medications
- Document subject's status as an outpatient, subsequently hospitalized, or died
- Perform clinical assessment to evaluate for increased severity of COVID-19 related symptoms
- Pregnancy test for women of child-bearing potential

9.2.5 Early Termination/Hospitalization

All subjects have the right to withdraw from study participation at any time during the study. If, for whatever reason, a subject withdraws from the study or is hospitalized, an Early Termination Visit will be performed.

The following procedures will be performed at the Early Termination Visit:

- Assess for adverse events
- Document all current medications, including medications over the counter and herbal medications
- Perform clinical assessment (as deemed feasible if hospitalized)
- Evaluate for increased severity of COVID-19 related disease
- Pregnancy Test for women of child-bearing potential

If clinical evaluation is deemed not feasible due to subject condition, the study team to collect Early Termination Visit data and attempt to collect Day 21 and Day 28 data and AE assessment for those subjects who are hospitalized and deemed off study.

9.2.6 Safety and Other Assessments

For Study procedures and evaluations to be done as part of the study to monitor safety and support the understanding of the study intervention's safety refer to Section of Schedule of Activities and Section of Study Assessments.

9.3 Adverse Events and Serious Adverse Events

Adverse event data will be summarized for all subjects from the date of informed consent. Site-reported serious adverse events and unexpected adverse drug reactions will be summarized as subject-based counts and percentages by AE category, MedDRA system organ class and preferred term. In addition, subject listings will be provided for serious, unexpected, and unanticipated adverse reactions. Any adverse events leading to discontinuation of study drug or death will also be listed for all subjects.

9.3.1 Definition of Adverse Event (AE)

An AE is defined as any unanticipated medical occurrence regardless to relationship of the investigative arm of the trial. An AE can be any unintended sign, lab abnormality, symptom, or disease associated with the trial. Any abnormality that presents during a medical test are to be defined as an AE if it produces clinical signs and/or symptoms, requires intervention, or deemed clinically significant by the Investigator.

9.3.2 Specific AEs to record

The *Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will* be utilized for AE reporting the following study- specific AEs:

- Cough
- Dyspnea
- Hypoxia
- Nausea
- Vomiting
- Abdominal pain
- Pruritus
- Loss of appetite
- Dizziness
- Skin rash

9.3.3 Definition of Serious Adverse Event (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of the Investigator, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Requires inpatient hospitalization or prolongs existing hospitalization
- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Medically important event by the Investigator (including any ED visit)
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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.

9.3.4 Definition of Unexpected Adverse Reaction (UAE)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Product Information/Summary of Product Characteristics). This would include any SAE on health or safety, any life-threatening problem or death caused by, or associated with a drug; or any other unanticipated serious problem associated with a drug that relates to the rights, safety, or welfare of subjects.

9.3.5 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether (or not) considered intervention-related (ICH E6(R2), Section 1.2).

9.3.6 Classification of an Adverse Event

9.3.6.1 Severity of Event

All AEs will be assessed by the study investigator using the CTCAE V. 5.0. Investigator or qualified designee will assess the severity of AEs using the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

9.3.6.2 Relationship to Study Intervention

Relationship to Study Products: All AEs must have their relationship to study intervention assessed by the investigator or qualified designee who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely:	The relationship of the AE and the drug or the study procedure can be established.
Probably:	While a clear relationship to the drug or to the study procedure cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.
Possibly:	There is no clear relationship between the AE and the drug or study procedure; however, one cannot conclude that there is no relationship.
Unrelated:	There is no relationship between the AE and the drug or study procedure. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced.

9.3.7 Expectedness

Study Team members who are clinically qualified (e.g., a physician, co-Investigator, sub-Investigator) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study products. This information will be provided to the IRB/IEC, and to any relevant governmental agency with regulatory or public health authority.

9.3.8 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care.

9.3.9 Capturing AEs

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, investigator's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

9.4 Adverse Event Reporting

Adverse event data will be summarized for all subjects in the safety population. Serious adverse events and unexpected adverse drug reactions will be summarized as subject-based counts and percentages by AE category. In addition, subject listings will be provided for serious, unexpected, and unanticipated adverse reactions. Any adverse events leading to discontinuation of study drug or death will also be listed for all subjects.

9.4.1 Serious Adverse Event Reporting

Study team members who are qualified will immediately report any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs must be reported in accordance with the protocol. Refer Section of Unanticipated Problems provides further detail.

9.4.2 Reporting Events to IRB/IEC

AEs, SAEs and Unanticipated problems (UPs) will be reported to IRB/IEC.

9.4.3 Events of Special Interest

N/A

9.4.4 Reporting of Pregnancy

Favipiravir has the potential for teratogenicity. In nonclinical reproductive and developmental toxicity studies, favipiravir was shown to be teratogenic in multiple animal species (mice, rats, rabbits and monkeys). Pregnancy status will be collected at the time of enrollment. Pregnancy testing for women of child bearing potential will occur on study days 1, 7 And 28. Any pregnancy that occurs during study days 1-28 will be followed, until the end, and reported to FDA and other regulatory authorities, where required.

9.5 Unanticipated Problems (UPs)

9.5.1 Definition of Unanticipated Problems (UPs)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)/ Independent Ethics Committee(IEC) approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing IRB/IEC. The UP report will include the following information:

1. Protocol identifying information: protocol title and number, PI's name, and the IRB/IEC project number;
   - A detailed description of the event, incident, experience, or outcome;
   - An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
   - A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

2. To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:
   - UPs that are SAEs will be reported to the IRB/IEC within 10 working days of the investigator becoming aware of the event.
   - A Study Team evaluation of an UP will be performed with a report of results of such evaluation will be provided to the reviewing IRB/IEC by the PI within 10 working days.

9.5.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed about UPs, and study-related results on an individual or aggregate level.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The primary efficacy objective of this study is to demonstrate that treatment with favipiravir in subjects with COVID-19 and mild-to-moderate symptoms will shorten the time to sustained clinical recovery ("component of the clinical outcome")." Primary efficacy endpoint: Time to sustained clinical recovery, defined as the time (number of days) from the start of the study treatment until symptom relief, evaluated from study day 1 onward.

10.2 Sample Size Considerations

10.2.1 Sample Size Determination: study's primary endpoint: time to sustained clinical recovery by Study Day 28

Group sample sizes of approximately 625 in each treatment group (Favipiravir and placebo) to get at least 815 clinical recoveries will achieve sufficient power to detect a clinically meaningful effect size using a two-sided Wilcoxon test at an overall significance level of 0.05.

10.2.2 Sample Size Justification: study's primary endpoint: time to sustained clinical recovery by Study Day 28

A review of the medical literature including descriptive and intervention studies reveals variation in the estimate of 'median time to symptom alleviation'. There is lack of consistency among studies in regard to: 1) the definition used for 'symptom alleviation', 2) the reference time point (some use the day of first symptoms, the day of first positive PCR test, the day of study enrollment, and the day of hospitalization, 3) the length of follow up. To account for the uncertainty surrounding the estimate of 'median time to symptom alleviation', we performed a series of intermediate sample size calculations for a variety of likely scenarios with median times to sustained clinical recovery for the control group ranging from 3 to 15 days and median times to sustained clinical recovery for the favipiravir group ranging from -1 to -6 days (when possible) as compared to the control group. The worst case of those scenarios was retained to establish the definitive sample size estimation for the trial.

The definitive sample size assessment is based on a group sequential design with a possibility to stop for efficacy and for futility (unbinding rule) at interim, once 45% of the information is obtained (i.e. 367 events), using Power family (Phi=1.147) alpha and beta spending functions. Assuming proportional hazards, a median time of 5 days in the control group vs. a median time of 4 days in the favipiravir group (which provide a hazards ratio of 1.25) and controlling for an overall alpha of 5% (two-sided), it is estimated that about 475 participants per group would be required to obtain a total of **815 clinical events** (defined as clinical recoveries). This will ensure a power of 85% to detect a difference between the two groups in terms of time to clinical recoveries by Day 28.

The unbinding futility rule uses a Power family beta spending function with Phi=1.147 and the probability to stop for futility at interim when there is no difference between the two groups (i.e. HR=1) is 73%.

The test for efficacy at interim uses a Power family alpha spending function with Phi=1.147 and if the hazard ratio is truly 1.25, the probability to conclude efficacy at interim is 49%.

This is to be noted that the futility rule is unbinding and that the recommendations whether or not to stop for futility will be done by the Data and Safety Monitoring Board (DSMB) (see section 5.5), upon review of the safety and efficacy data, and not solely based on the futility rule.

10.2.3 Sample Size Determination: Sub-study's Viral Shedding Endpoint: Time to undetectable viral shedding by study day 10

Group sample sizes of approximately 275 subjects in each treatment group (Favipiravir and placebo) in order to obtain 112 undetectable viral shedding events will achieve sufficient power to detect a clinically and epidemiologically meaningful effect size using a two-sided Wilcoxon test at a significance level of 0.05.

10.2.4 Sample Size Justification: Sub-study's Viral Shedding Endpoint: Time to undetectable viral shedding by study day 10

To calculate the required sample size, we used the following assumptions: 1) Follow-up duration per patient of 10 days, 2) Alpha of 0.05, 3) Lost to follow up of 0, 4) Exponential survival rates, 5) Median

time to sustained clinical recovery for the control group of 5 days, 6) Median time to sustained clinical recovery for the favipiravir group of 2.9 days.

In order to detect as statistically significant difference in the median time to undetectable viral shedding of 5 vs. 2.9 days in the control vs. favipiravir group, respectively (HR = 1.7), it is estimated that a total of about 550 subjects (275 per treatment group) in order to obtain 112 clinical events defined as undetectable viral shedding events would be required to achieve a power of 80%.

10.3 Populations for Analyses

- Modified-Intention-to-Treat (mITT) Analysis Dataset includes all randomized subjects who took at least one dose of study medication (excluding subjects who qualified for enrollment based upon changes in taste and smell). Some of these subjects were included on a previous version of the protocol when the loss of smell or taste was considered as one of the symptoms to be alleviated.
- Modified-Intention-to-Treat 2 (mITT2) Analysis Dataset includes all randomized subjects who took at least one dose of study medication and report (in ePRO) sufficient protocol-mandated COVID-19 symptoms (excluding taste and smell), defined as 2 or more symptoms worse than mild on study day 1. Some of these subjects were included on a previous version of the protocol when the loss of smell or taste was considered as one of the symptoms to be alleviated.
- Intention-to-Treat (ITT) Analysis Dataset includes all randomized subjects.
- Safety Analysis Dataset includes subjects who took at least one dose of study intervention.
- Per-Protocol Analysis Dataset: subset of the subjects in the mITT2 set who took at least 80% of study intervention and had no protocol violations that would affect the primary efficacy endpoint. Such protocol violations include treatment with high dose steroids, remdesivir, or SARS-CoV-2 monoclonal antibodies.
- Other Datasets that may be used for sensitivity analyses

10.4 Statistical Analyses: General Approach

Baseline demographic and clinical characteristics and other results will be summarized using descriptive summary statistics. Data collected in the trial will be summarized overall and by treatment arm.

Survival analysis techniques will be used to analyze the time-to-event variables. Failure curves will be constructed for time to positive event using Kaplan-Meier estimates. Time to sustained clinical recovery will be compared using a Gehan Wilcoxon test which gives more weight to early events. Time to a negative event (such as time to death, time to hospitalization) will be compared using the Log-rank test for comparison of survival distributions. Summary tables for safety and efficacy endpoints will include event rates (Kaplan-Meier estimates of event rates), relative risk, confidence interval for the relative risk, the difference in means/rates, the confidence interval for difference in means/rates, and the p-value.

For categorical variables, results within each arm will be summarized with subject counts, percentages, and 95% confidence intervals. The differences between the two treatment arms will be summarized with the difference in percentages and the asymptotic 95% confidence interval for the difference of two percentages.

10.5 Analysis of the Primary Efficacy Endpoint(s)

For the primary efficacy endpoint, time to sustained clinical recovery from study day 1 onward will be compared using a Gehan Wilcoxon test.

The primary analysis of the primary efficacy endpoint will be based on the Modified Intent to Treat Population (mITT), defined as any subject randomized into the study and took at least on dose of study medication (excluding subjects who qualified for enrollment based upon changes in taste and smell).

Additional primary efficacy endpoint analyses will also be performed using the mITT, mITT2, and the Per Protocol populations. Every effort will be made to ensure that subjects are followed until hospitalization, death, or 28 days post treatment start, whichever happens first. Subjects who were hospitalized or died will be assumed to have not met the primary endpoint in the primary analysis.

10.6 Analysis of the Key Secondary Endpoint(s)

Proportion of subjects with COVID-19 progression will be presented with counts and percentage. Significance among group will be evaluated using Chi-square test or fisher test as applicable. The corresponding confidence interval for the difference in proportions will be calculated.

Viral shedding sub-study (time in number of days to negative conversion of detectable SARS-CoV-2 viral RNA to undetectable viral RNA in RT-PCR assays of saliva, from start of study treatment to date of last viral assessment) will be analyzed using time-to event methods.

All secondary endpoint analyses will be performed for the mITT, mITT2 and PP populations.

Adjustment for multiple testing will be performed to control the overall type 1 error to no more than 5% for the interim and final analysis on the primary efficacy endpoint.

Moreover, for labeling purposes, a hierarchical approach will be used to control the overall type 1 error to ≤ 5% for the primary and key secondary endpoints. The order of testing will be:

1. Clinical recovery
2. Broad progression (key secondary endpoint)
3. Narrow progression (key secondary endpoint)

Statistical significance cannot be claimed if the parameter on top of the parameter being tested did not reach statistical significance. For example, if clinical recovery was not statistically significant at final analysis, the other parameters will not be considered as having reached statistical significance (no matter the results obtained). If clinical recovery reaches statistical significance at final analysis and Broad progression (key secondary endpoint) does not, the remaining parameters will not be considered as having reached statistical significance and so on.

10.6.1 Additional Secondary Efficacy Analysis

The additional secondary endpoint of time to negative conversion of positive SARS-CoV-2 (viral culture assays of saliva) will be analyzed as described in the statistical analysis plan (SAP version 3.1).

The additional secondary endpoint analyses will be performed for the mITT, mITT2, and PP populations.

10.7 Safety Analyses

Adverse event data will be summarized by treatment group for subjects in the safety population. Safety will be evaluated by presenting summaries of treatment emergent AEs by system organ class and preferred term. Drug related TEAEs, discontinuation of study medication due to TEAEs and all SAEs will also be summarized.

In addition, subject listings will be provided for serious, unexpected, and unanticipated adverse reactions. Any adverse events leading to discontinuation of study drug or death will also be listed for all subjects.

10.8 Other prespecified analyses

10.8.1 Baseline Descriptive Statistics

Demographic characteristics and medical history, adverse events, COVID-19 disease signs and symptoms and treatment compliance will be summarized and compared between treatment groups. The details of the statistical analyses are included in the Statistical Analysis Plan (SAP 3.1).

10.8.2 Planned Interim Analyses

The DSMB will also review the results of the first interim analysis for futility and efficacy once 45% of the clinical events (i.e. 367 clinical recoveries) are obtained and once 45% of the patients are recruited.

The nominal alpha of 0.02 and of 0.0369 at the time of interim and final analysis, respectively. A p-value less than 0.02 (interim) or 0.0369 (final) will be considered to be statistically significant.

Futility will be concluded at interim on the primary efficacy endpoint if Z-value is smaller than 0.58964 (i.e. p-value is larger than 0.6389).

10.8.3 Sub-Group Analyses

1) Status at enrollment defined as Seronegative (negative IgG) vs. Seropositive (positive IgG).
2) Age at enrollment: Age ≥ 50 years vs. Age <50 years and Age ≥ 60 years vs. Age <60 years.
3) Time from first positive SARS-CoV-2 test to enrolment (<2 days from their first positive COVID test vs. >2 days).
4) Risk-status of COVID-19 progression (high risk vs. others). High-risk for COVID-19 progression is defined as patients who meet at least one of the following criteria: 1) Overweight (BMI ≥25), 2) Chronic kidney disease, 3) Diabetes Mellitus, 4) Weakened immune system, 5) Currently receiving immunosuppressive treatment, 6) ≥65 years of age, 7) Pregnancy, 8) Cardiovascular disease/hypertension, 9) Chronic lung disease, 10) Sickle cell disease, 11) Neurodevelopmental disorders, 12) Medical-related technological dependence
5) Ethnicity (Hispanic vs. non-Hispanic).
6) Magnitude of symptoms at enrollment (high, defined as having a minimum of 4 symptoms at a level of moderate or severe on study day 1 vs. low, defined as having <4 moderate or severe symptoms on study day 1).

7) Status of receiving SARS-CoV-2 monoclonal antibodies treatment after study enrolment (Yes, No).
8) Status of study-drug adherence (drug adherence >80% defined as: the subject took at least 72 study-drug pills as documented in ePRO and/or EDC vs. ≤ 80%). For calculation purposes: day 1 dose 1 and dose 2 are 9 pills each, all other study doses are 4 pills.
. Detailed analysis will be described in SAP.
9) Level of highest RNA load on study day 1 or 2 or 3: high versus vs. all other and very high versus all other. High and very high RNA loads are defined as RNA load of >1,000 or >10,000, respectively.
10) Type of SARS-CoV-2 variant: Alpha (B.1.1.7), Beta (B.1.351, B.1.351.2, B.1.351.3), Delta (B.1.617.2, AY.1, AY.2, AY.3), or Gamma (P.1, P.1.1, P.1.2).
11) Status of C-reactive Protein level (abnormally elevated vs. normal) at baseline.
12) Status of D-dimer level (abnormally elevated vs. normal) at baseline.
13) Status of C-reactive Protein level and D-dimer (both are abnormally elevated vs. other) at baseline.

10.8.4 Tabulation of Individual subject Data

N/A

10.8.5 Sensitivity Analysis

All subjects with an initial recovery who later relapsed within the 28-day period labeled as not meeting the primary endpoint. Detailed list of all sensitivity analyses is described in the SAP 3.1.

10.9 Exploratory Analyses

Exploratory endpoints are related to proportion of subjects and will be presented with counts and percentage. Significance among group will be evaluated using Chi-Square test or Fisher test as applicable. The corresponding confidence interval for the difference in proportions will be calculated.

A detailed description of all statistical analyses is described in the SAP 3.1**.**

11.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical, and Study Oversight Considerations.

11.1.1 Informed Consent Process

11.1.1.1 Consent/assent and Other Informational Documents Provided to subjects

Consent describing in detail the study intervention, study procedures, and risks will be provided to the subject and documentation of informed consent will be required prior to administering study interventions.

11.1.1.2 Consent Procedures and Documentation

Informed consent (IC) is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The investigator will explain the research study to the subject and answer any questions that may arise. The explanation will be provided

in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Potential subjects will have the opportunity to ask questions. The subjects will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. They will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

FDA regulations generally require that the informed consent of a trial subject be documented by the use of a written consent form that has been approved by the IRB/IEC and signed and dated by the subject at the time of consent (21 CFR 50.27(a)). Considering COVID-19 infection control measures, if the technology is available, current FDA guidance suggests that electronic methods of obtaining informed consent should be considered as follows:

- To ensure that subjects are approached in a consistent fashion, a standard process should be used that will accomplish the following:
    1. Identification of who is on the call or telemedicine visit
    2. Review of the Informed Consent with the subject by the investigator (or their designee) and response to any questions the subject may have
    3. Confirmation by the witness that the subject's questions have been answered
    4. Confirmation by the investigator that the subject is willing to participate in the trial and sign the informed consent document while the witness is listening on the phone
    5. Verbal confirmation by the subject that they would like to participate in the trial and that they have signed and dated the informed consent document that is in their possession.

- If the signed informed consent document cannot be collected from the subject's location and included in the study records, FDA considers the following option acceptable to provide documentation that the subject signed the informed consent document:
    1. A dated attestation by the witness who participated in the call and by the investigator that the subject confirmed that they agreed to participate in the study and signed the informed consent.

For this study involving subjects with COVID-19 positivity, in accordance with FDA guidance, the following steps will be performed while obtaining the IC by phone or telehealth video chat from the Subject.

- Purpose of the study and the potential risks/benefits of the use of the Investigational Agent favipiravir in the treatment of confirmed COVID-19 infection will discussed in detail by the principal investigator or qualified designee (PI/ designee) with the subject prior to obtaining the IC. Opportunity to review the ICF (informed consent form) prior to or during the discussion will be provided. Adequate time for discussion between the PI or qualified designee will be given to the potential subject. After review of the IC, any questions that the potential subject have will be addressed during or after review of the IC.

- Availability and/or possibility of other potential treatment options will be discussed with the subject.

- A second member of the study team will be present on the phone or video chat during the entire discussion. The witness will ask the potential subject if they understand the contents of the discussion and if they have any questions to address. The subject will be informed that they can ask questions at any time during the trial.

- The PI or qualified designee will sign the ICF along with the witness. Copies of the signed form will be placed in the subject's medical record

- This document will be placed into the electronic medical record and electronically signed, and time stamped by the investigator. In de-identified form, it will be the study source document for documenting the process of obtaining ICF. A copy of the electronically signed consent (signed by the witness and investigator) is either emailed or sent by US Mail.

11.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and the IRB/IEC.

11.1.3 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible. The use of the telemedicine video platform will include subject instruction on using the platform in a private setting or with a family member/ significant other via Facetime as described in the Study Intervention.

Representatives of the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC and Institutional policies.

The Principal Investigator will be responsible to ensure the study is conducted in accordance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and that the data recorded is valid. To achieve this objective, the study will be continuously monitored, and the study conduct reviewed on a weekly basis by the Study Team.

Monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

A Clinical Monitoring Plan will be created by the Study Team and will describe in detail the personnel who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

11.1.4 Future Use of Stored Specimens and Data

The collection of personal subject information will be limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

Data from the EDC will be exported into Excel or SAS file format (password protected), which will then be used for data analysis. Only de-identified, not including the subject's contact or identifying information data will be used for data analysis.

11.1.6 Safety Oversight

In addition to the Principal Investigator's responsibility for overall study oversight, safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB are independent from the study conduct and free of conflict of interest. The DSMB will operate under the rules of an approved charter written and reviewed at the organizational meeting of the DSMB. After the organization meeting, the DSMB will meet as outlined in the charter. The final meeting scheduled will be outlined in the charter. The DSMB will also review the results of the interim analysis for efficacy described in section of "Statistical Considerations". Stopping rules for safety and efficacy will be specified in the charter.

11.2 Clinical Monitoring

Clinical monitoring will be conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the

trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

11.2.1 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to study PI or designee for resolution.

Following written Standard Operating Procedures (SOPs), the PI and study team will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all source data/documents, and reports for the purpose of monitoring, auditing and inspection by local and regulatory authorities.

11.3 Data Handling and Record Keeping

11.3.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the Study Staff under the supervision of the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Any hardcopies of study visit worksheets will be provided for use as source document worksheets for recording data for each subject enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from study source documents will be consistent with the data recorded on the source documents.

Clinical data AEs, concomitant medications and any other data collected from subjects will be entered into a 21 CFR Part 11 ready data capture system. The data system includes an audit trail, password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

11.3.2 Study Records Retention

Data from the study will be maintained for two (2) years after the date the investigation is completed, terminated or until the records are no longer required to support the protocol, whichever date is later. Custody of the records may be transferred. Subject records and data are eligible for inspection and/or copying by applicable regulatory authorities.

11.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The

noncompliance may be either on the part of the subject, the Investigator, or the Study Team. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations will be summarized by type of deviation and treatment group. Protocol deviation summaries will be subject based.

11.5 Publication and Data Sharing Policy

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

11.6 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.7 Additional Considerations

N/A

12.0 Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan

COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IP	Investigational Product
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
IEC	Independent Ethics Committee
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IWRS	Interactive Web Randomization System
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities

SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

13.0 Protocol Amendment History

The table below is intended to capture key changes made between protocol version 5.0 and 5.1

Version 5.0	Version 5.1	Rationale
Site-Subject Remote Visits on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 17, 21, 24 and 28	Site-Subject Remote Visits on Days 1, 3, 5, 7, 9, 14, 17, 21, 24 and 28	Change made to address FDA concerns related to site-subject interactions (protocol versions 4.0 and 5.0 have never been implemented). The change reflects protocol version 3.0 which was the last version implemented during the study.
It is the site responsibility to ensure patients are properly trained on the ePRO requirements and assist the subjects with completing the ePRO diary during the Day 1 visit. Subject interactions will happen on Days 2 through 12, as well as 14, 17, 21, 24, and 28. During the site and subject interactions, the site staff will review the ePRO content for completeness and will work with the subject to ensure complete data entry. This includes reviewing each COVID-19 symptom for severity, temperature, O2 saturation, review of AEs, concomitant medications, IP compliance and saliva sampling compliance (when applicable). Beyond Study Day 12, in the case that subject has not reported on ePRO on a day that a subject visit is not scheduled, the study team will call the subject (unscheduled visit) and ensure that the subject enters the missing information during the phone call. However, if the ePRO system is unavailable or not accessible by the subject for any reason, then the subject should record their information on the paper diary for those days. If the subject used paper diary, during the next site and subject interaction, site staff should complete the data entry on behalf of the subject in ePRO. The study team will collect the paper diary from the subject after they either meet the clinical recovery or the subject reaches Day 28.	The study team will be reviewing the data reported by subject to ensure compliance, accuracy and completeness on days 1, 3, 5, 7, 9, 10, 14, 17, 21, 24, and 28. Beyond Study Day 10, once the subject meets the primary efficacy endpoint, the subject is not required to continue the self-assessment and reporting of COVID-19 symptoms. However, the study team, during the remote patient visits will evaluate and report the severity of COVID-19 associated symptoms as per the set frequency mentioned in the table.	
	Removed: While collecting adverse events, subjects will be asked whether or not any of their adverse events resulted in an emergency department (ED) visit. In cases where this has occurred, the date of the visit will be recorded, the reason for the visit (i.e. - COVID-19 associated symptom or not), and the adverse event(s) which prompted the visit. Because ED visits are considered to be a medically-important event determining in part the subject's COVID progression, ED visits for any cause will be documented as SAEs.	The change reflects protocol version 3.0 which was the last version implemented during the study.
From: Primary Efficacy Endpoint:	To: Primary Efficacy Endpoint:	In accordance with FDA guidance

The endpoint will be considered to have been met at the earliest time point from study day **1** onward at which the subject has reached Sustained Alleviation of Symptoms as defined by:	The endpoint will be considered to have been met at the earliest time point from study day **3** onward at which the subject has reached Sustained Alleviation of Symptoms as defined by: Added: (COVID-19 symptoms can be missing for 1 of the first two sustainability days but not for the last day of sustainability)	In accordance with FDA guidance
	Change in the Viral Load threshold from 100 RNA copies to 15 RNA copies (the detectability threshold) .	In accordance with FDA guidance
Modified-Intention-to-Treat (mITT) Analysis Dataset includes all randomized subjects who took at least one dose of study medication and report (in ePRO) sufficient protocol-mandated COVID-19 symptoms (excluding taste and smell), defined as 2 or more symptoms worse than mild on study day 1. Some of these subjects were included on a previous version of the protocol when the loss of smell or taste was considered as one of the symptoms to be alleviated.	mITT Population changed to include all randomized and treated subjects regardless of their Day 1 ePRO entries. The original mITT population as described in Protocols V4.0 and V5.0 is now named mITT2. mITT2 is used for exploratory and sensitivity analyses. Addition of exploratory and sensitivity analyses.	In accordance with FDA guidance
	Slight change in the definition of the sub-group that is at high risk for COVID-19 progression	To reflect the current definition used by FDA

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Preseco Protocol V5.1_2021-11-03_Clean_FINAL

Final Audit Report 2021-11-04

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