FAVIPIRAVIR

GPL/CT/2020/002/III

A RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FAVIPIRAVIR COMBINED WITH STANDARD SUPPORTIVE CARE IN ADULT INDIAN PATIENTS WITH MILD TO MODERATE COVID-19

Phase of Development	Phase 3
Sponsor	Glenmark Pharmaceuticals Limited, India
Protocol Number	GPL/CT/2020/002/III
Approved by	Dr. Monika Tandon Vice President & Head, Clinical Development
Protocol Version	Version 3.0
Date	26-Apr-2020
Supersedes	Version 2.0 dated 23-Apr-2020

This study must be conducted in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigational Brochure (IB) for favipiravir. I have read the GPL/CT/2020/002/III and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Name of Investigator

_____

Signature of Investigator

_____

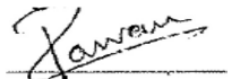
Date

SPONSOR'S SIGNATURE

This protocol reflects the Sponsor's current knowledge of favipiravir as applicable to this study. It has been designed to achieve the stated objectives while minimizing exposure to, and risk from, both the products being used and the assessments. The assessments are all considered to be appropriate, capable of validating the stated objectives of the study, and of providing the necessary information to ensure subject safety. The protocol has been designed according to the principles of the ICH guidelines for GCP, and the Declaration of Helsinki. It has undergone both medical and scientific review by the Sponsor. The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the case report forms (CRFs).

- We hereby agree to conduct the study in accordance with this protocol and the above-mentioned guidance/ regulation.
- We agree to comply with all relevant standard operating procedures (SOP) required for the conduct of this study.
- We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

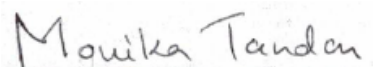
Signed on behalf of the Sponsor, Glenmark Pharmaceuticals Limited.



Dr. Pawan Singh

Deputy General Manager | Clinical Development
Glenmark Pharmaceuticals
Andheri East, Mumbai- 400099
E-mail: pawan.singh@glenmarkpharma.com
Date: 19 Apr 2020

Date: 26-Apr -2020



Dr. Monika Tandon

Vice President Clinical Development,
Glenmark Pharmaceuticals
Andheri East, Mumbai- 400099
E-mail: Monika.Tandon@glenmarkpharma.com
Date: 19 Apr 2020

Date: 26-Apr -2020

2. SYNOPSIS

Name of Sponsor/Company: Glenmark Pharmaceuticals Ltd.

Name of Study Drug: Favipiravir

Title of the Study: A Randomized, Open-Label, Multicenter Study To Evaluate The Efficacy And Safety Of Favipiravir Combined With Standard Supportive Care In Adult Indian Patients With Mild To Moderate COVID-19.

Protocol Number: GPL/CT/2020/002/III

Phase of development: Phase 3

Indication: Treatment of mild to moderate COVID-19.

Study Rationale:

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide. As of April 19, 2020, there have been 2.3 million reported cases worldwide. Importantly as of April 19, 2020, India reported total confirmed cases of 15,712 with 507 fatalities as per data of Ministry of Health, Govt of India. It is widely known and acknowledged that , numerous antiviral agents, immunotherapies, and vaccines are being investigated as potential therapies, however, so far, none have been approved for COVID-19 and hence there is no specific/ approved treatment for COVID-19 anywhere in the world. Antiviral agents that have a strong rationale for efficacy have been being evaluated in the pandemic to repurpose drugs with the aim of reducing mortality and morbidity.

Favipiravir has a mechanism that prevents the propagation of RNA viruses, and is a reserve drug for pandemics associated with novel Influenza infections. It is also effective on a wide range of RNA viruses (including arenaviruses, phleboviruses, hantaviruses,flaviviruses, enteroviruses, respiratory syncytial virus, and noroviruses) including SARS CoV 2 and is undergoing clinical evaluation in COVID-19 pandemic in many countries.

Two recently completed clinical studies of favipiravir have been published indicating efficacy of favipiravir in COVID-19 patients. In one of the published studies conducted in China (favipiravir versus arbidol for COVID-19: A Randomized Clinical Trial; https://doi.org/10.1101/2020.03.17.20037432) approximately 240 subjects were randomized and favipiravir was compared against umifenovir; favipiravir can be considered as a preferred treatment because of its' higher 7 day's clinical recovery rate (71.43%) than umifenovir (55.86%) and the time of cough relief and fever reduction of favipiravir was significantly shorter than that of umifenovir. In another open label study; favipiravir has proven to be superior to lopinavir/ritonavir in treatment of COVID-19 positive patients conducted in Wuhan, China. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir. A shorter viral clearance time was found for the favipiravir arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d, $P < 0.001$). The favipiravir arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% versus 62.22% ($P = 0.004$). Multivariable cox regression showed that favipiravir was independently associated with faster viral clearance. No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group. It is currently being evaluated both in mild and in moderate COVID-19 as it is postulated that because of the specific antiviral activity; favipiravir can potentially kill the virus at an early stage of infection when the symptoms are mild to moderate and prevent progression of disease. Time from infection to randomization is emerging as an important factor in antiviral administration. The impact on reduction in disease duration is highest when taken as early as possible.

Favipiravir is an already approved drug in Japan since 2014 (Avigan Tablets, Toyama Chemical Co., Ltd.), for the treatment of the new or re-emerging pandemic influenza virus infections. Favipiravir was also approved for treatment of novel influenza on February 15, 2020 in China . It is a reserve drug stockpiled for novel pandemics and is currently being considered as a potential treatment option in patients having mild to moderate COVID-19. On 22 March 2020, Italy has approved favipiravir for experimental use against COVID-19 and has begun conducting trials in 3 regions most affected by the disease. Favipiravir is undergoing multiple clinical trials globally in USA, EU and Japan in mild to moderate Covid-19 and is being evaluated as a treatment option for SARS-CoV-2.

Glenmark proposes to conduct the current study of favipiravir in mild to moderate COVID-19 patients in India in line with global trials ongoing for this drug.

Objectives:

Primary:

- The primary objective of this study is to evaluate the clinical efficacy of favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

Secondary:

- The secondary objective is to evaluate the safety and tolerability of favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

Study population: Patients admitted to hospital with mild (including asymptomatic) to moderate COVID-19 (confirmed by RT-PCR).

Study design: This is a randomized, multi-center, open-label, parallel arm, clinical study in Indian patients evaluating the efficacy and safety of favipiravir with standard supportive care vs standard supportive care alone in mild to moderate COVID-19.

It is a parallel arm study with stratified randomization in which 150 eligible patients will be randomized in a 1:1 ratio into 2 groups: one group will receive favipiravir along with standard supportive care and the control group will receive standard supportive care in accordance with latest guidelines issued by Ministry of Health and family welfare; Government of India. Treatment duration is a maximum of 14 days and the total study duration will be maximum for 28 days from randomization. The randomization will be stratified based on baseline disease severity into mild and moderate COVID-19 cases so that 90 subjects of mild and 60 subjects of moderate COVID-19 will get randomized into each strata. All the subjects will be hospitalized as per current standard of treatment and will be discharged only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative and clinical cure is achieved

Study Endpoints:

Primary Endpoint:

- Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days]
  (Time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab).

Secondary Endpoints:

- Time from randomization to clinical cure based on clinician assessment (Recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours; defined as(axillary temperature $\leq$ 97.8°F; respiratory rate $\leq$ 20 times/min; Oxygen saturation $\geq$ 98% without oxygen supplementation; mild or no cough).*
- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge
- Frequency of serious adverse events

  Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier.

  *For those patients who presented with clinical signs and symptoms at baseline.

Number of subjects (planned): 150 subjects with mild to moderate COVID-19 will be randomized in the study in a 1:1 ratio to favipiravir with standard supportive care or standard supportive care. 90 subjects with mild COVID-19 and 60 subjects of moderate COVID-19 will be randomized in the study.

Main criteria for inclusion:

1. Voluntarily participating in the clinical study; fully understanding and being fully informed of the study and having signed the Informed Consent Form (ICF); willingness and capability to complete all the study procedures
2. Age 18-75 years (inclusive) at the time of signing ICF
3. Patients with laboratory confirmation of infection with SARS-CoV-2 by positive RT-PCR (within 48 hours prior to randomization)
4. For female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pretreatment serum or urine pregnancy test
5. Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment;
6. Not participating in any other interventional drug clinical studies before completion of the present study.

Additional Inclusion criteria for mild cases only:

7. Time interval between symptoms onset and randomization to no more than 7 days
8. Pyrexia (temperature < 102.2°F); respiratory rate 12 to ≤20/min.
9. No more than four of the following of mild severity, and no more than two of moderate severity (Mild is defined as symptoms not requiring any or minimal therapeutic intervention; moderate is defined as symptoms which produce small impairment of function and require some form of therapeutic intervention; severe is defined as symptoms resulting in marked impairment of function):
    - Cough
    - Sore throat
    - Headache
    - Nasal congestion
    - Body aches and pains
    - Fatigue

Additional Inclusion criteria for moderate cases:

10. Patients with the interval between symptoms onset and randomization is no more than 10 days
11. Chest imaging (CT as first option or X-ray if CT not possible)-documented pneumonia
12. Patients with pyrexia (axillary ≥98.6°F or oral ≥99.5°F); respiratory rate >20 to <30/min

Exclusion criteria:

1. Where, in the opinion of the investigator, participation in this study will not be in the best interest of the subject, or any other circumstances that prevent the subject from participating in the study safely
2. Severe infection, defined as need for invasive or non-invasive ventilator support, ECMO or shock requiring vasopressor support.
3. Inability to intake or tolerate oral medications.
4. Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN
5. Gout/history of gout or hyperuricemia (above the ULN)
6. Prolonged QT, defined as QTcF ≥450 milliseconds for men and as QTcF ≥470 for women
7. Known severely reduced LV function (Ejection fraction <30%)
8. Oxygen saturation (SPO2)≤93% or arterial oxygen partial pressure (PaO2)/ fraction of inspired O2 (FiO2)≤300 mmHg;
9. Requires ICU care for management of ongoing clinical status.
10. Known allergy or hypersensitivity to Favipiravir;
11. Known severe renal impairment [creatinine clearance (CrCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis;
12. Asthma or chronic obstructive lung disease

13. Psychiatric disease that is not well controlled (controlled defined as stable on a regimen for more than one year).
14. Pregnant or lactating women;
15. Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug.
16. Clinical prognostic non-survival, palliative care, and have no response to supportive treatment within three hours of admission.

Duration of study participation: Maximum of 28 days from randomization

Duration of treatment: Maximum of 14 days of treatment in subjects with mild to moderate COVID-19.

Investigational product, dosage and mode of administration: Favipiravir tablets**;** 3,600 mg (1,800 mg BID) (Day 1) + 1,600 mg (800 mg BID) (Day 2 or later) for up to maximum of 14 days, along with supportive care.

Reference therapy, dosage and mode of administration: Standard supportive care alone.

Criteria for evaluation:

Efficacy:

Primary Endpoint:

- Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days]
  (Time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab).

Secondary Endpoints:

- Time from randomization to clinical cure based on clinician assessment (Recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours; defined as(axillary temperature ≤ 97.8°F; respiratory rate ≤ 20 times/min; Oxygen saturation ≥ 98% without oxygen supplementation; mild or no cough).*
- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge

  Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier.

  *For those patients who presented with clinical signs and symptoms at baseline.

Safety:

- Frequency of serious adverse events.

Study Populations:	**All Patients Set** All randomized patients will be included in the All Patients Population. All data listings will be based on this population. Where listings are separated by treatment arm, safety data listings will be grouped by actual study treatment received and all other listings will be grouped by treatment randomized. Given that only randomized patients are entered onto the study database, it is implicit that the All Patients Population will comprise all patients in the study database. **Intent-to-Treat (ITT) Set** All randomized patients will be included in the intent-to-treat (ITT) population. All efficacy analyses will be based on the treatment arm to which the patients were randomized. Given that only randomized patients are entered onto the study database, it is implicit that the ITT Population will comprise all patients in the study database. The ITT population is the same as the All Patients population used for data listings, where data are reported by randomized treatment. **Per protocol analysis set (PPS)** A per protocol analysis population is not being defined for this study. The protocol violations will be documented according to the inclusion and exclusion criteria to be used as information in the Clinical Study Report (CSR). The only major protocol violation defined for this study is no study medication taken, which will lead to exclusion from the Safety Analysis Population. Violations of protocol-defined inclusion/exclusion criteria and on-study protocol violations will be classified as minor violations, and will not lead to exclusion from any analysis population. **Safety Analysis Set (SAS)** All patients randomized who have received any amount of study medication will be included in the Safety Analysis Set (SAS). By assumption patients who have received any amount of study medication are assumed to have had the opportunity to report adverse event safety data regardless of whether they have any post-baseline safety assessments recorded and will be included in the SAS. All safety analyses will be based on the treatment the patients actually received such that a patient who received any dose of Favipiravir will be included in the Favipiravir arm (regardless of whether this was intended). **Other Analysis Populations** No additional analysis populations are defined. However, it should be noted that for certain outcomes, the analysis may be based on sub-sets of the ITT population, as the outcome may only be relevant for specific patients. For objective response rate and time to response, only patients with measurable disease at baseline will be included in the analysis. **Outputs by Treatment Received** If any patients are randomized but not treated, listings produced for all patients by treatment received will include patients under the category 'Treatment Not Given'. Patients who receive one or more administrations of Favipiravir at any time during the study will be reported under 'Favipiravir' arm as opposed to 'Standard Supportive Care' arm even if this administration was given in error (i.e. the patient was randomized to receive placebo but received one or more doses of Favipiravir).

Determination of Sample Size:	Based on the hazard ratio (HR) of 3.434 in the paper by Q. Cai et al, total 28 viral clearance events (i.e. viral clearance patients) in each population need to be observed in order to obtain 90% power, a sample size of 40 to 100 is required in each mild and moderate population. In accordance with regulatory recommendations 90 subjects will be enrolled in mild Covid-19 sub-group and 60 subjects will be enrolled in moderate Covid-19 subgroup and a total sample size of 150 will be enrolled in the study.
Efficacy Analyses:	***Analysis of Primary Efficacy Endpoint*** The primary endpoint will be analyzed using the Kaplan-Meier method and log-rank test. Potential influencing factors of viral clearance will be analyzed by Cox regression model. In the Cox model, the time of viral clearance was set as the Time variable, viral clearance (0 = no, 1 = yes) was set as the status, and the variables including age and independent variables. Sub-group analysis will be done for the mild and moderate population for the primary endpoint. ***Analysis of Secondary Efficacy Endpoints*** The following time event endpoints will be analyzed the same way as the primary endpoint using the Kaplan-Meier method, log-rank test and Cox analysis. • Time from randomization to clinical cure based on clinician assessment (Recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours) defined as (axillary temperature ≤ 97.8°C; respiratory frequency ≤ 20 times/min; Oxygen saturation ≥ 98% without oxygen inhalation; mild or no cough).* • Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation • Time from randomization to hospital discharge Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier. The following time event endpoints will be analyzed using the chi-square test or Fisher's exact test. • Rate of Clinical cure at day 4/7/10/14 • Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14 Sub-group analysis will be done for the mild and moderate population for secondary efficacy endpoints.
Safety Analyses:	The analysis of safety and tolerability will be based on the safety analysis set. Safety data during the 14-day treatment period will be evaluated and summarized descriptively. Adverse events will be summarized by system organ class and preferred term. Subjects will be counted only once for each preferred term, system organ class, and by the highest severity of an event. Laboratory evaluations will be summarized with descriptive statistics at each visit, and change from baseline summarized for each post-baseline visit. Laboratory measurements will also be summarized. ECG, vital signs (pulse, RR, temperature and BP), and physical examination will be summarized. Details will be presented in the SAP.
Interim analyses:	Early readouts of efficacy and safety may be performed after minimum 14 events of viral clearance (RT PCR negative) in about 30 subjects.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBC,	complete blood count
CRF	case report form
CSR	clinical study report
COVID-19	coronavirus disease of 2019
CrCl	creatinine clearance
CT	computerized tomography
CXR	chest X-ray
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	electronic case report form
FiO2	fraction of inspired O2
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IQR	Interquartile range
IEC	independent Ethics Committee
IRB	Institutional Review Board
(IVRS/IWRS)	(interactive voice response system/interactive web-based response system)
LAR	legally acceptable representative
LDH	lactic acid dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MV	mechanical ventilation
NIV	Non-invasive ventilation
PaO2	arterial oxygen partial pressure

Abbreviation or Specialist Term	Explanation
QT	Electrocardiographic QT interval from onset of Q wave to end of T wave
QTc	QT interval corrected for HR
RT-PCR	Reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SpO2	peripheral capillary oxygen saturation
ULN	Upper limit of normal

5. INTRODUCTION

5.1. Background Information

The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment. The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide. As of April 19, 2020, there have been 2.3 million reported cases worldwide. Importantly as of April 19, 2020, India reported total confirmed cases of 15,712 with 507 fatalities as per data of Ministry of Health, Govt of India. This novel Betacoronavirus is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV); based on its genetic proximity, it likely originated from bat-derived coronaviruses with spread via an unknown intermediate mammal host to humans. The viral genome of SARS-CoV-2 was rapidly sequenced to enable diagnostic testing, epidemiologic tracking, and development of preventive and therapeutic strategies (Sanders JM, 2020).

It is widely known and acknowledged that today, numerous antiviral agents, immunotherapies, and vaccines are being investigated as potential therapies, however, so far, none have been approved for COVID-19 and hence there is no specific/ approved treatment for COVID-19 anywhere in the world. Therefore, antiviral agents that have a strong rationale for efficacy have been being evaluated in the pandemic to repurpose drugs with the aim of reducing mortality and morbidity

Favipiravir has a mechanism that prevents the propagation of RNA viruses, and is a reserve drug for pandemics associated with novel Influenza infections. It is also effective on a wide range of RNA viruses (including arenaviruses, phleboviruses, hantaviruses, flaviviruses, enteroviruses, respiratory syncytial virus, and noroviruses) including SARS CoV 2 and clinical data emerging from trials in China in the current pandemic has generated interest globally and is undergoing clinical evaluation in COVID-19 pandemic in many countries including US, EU and Japan.

5.2. Nonclinical Experience

An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The 2019-nCoV belongs to Betacoronavirus which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. In one study, the antiviral efficiency of five FDA-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS- 5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro was evaluated. In this study favipiravir has been shown to be 100% effective in protecting mice against Ebola virus challenge and its EC_{50} value in Vero E6 cells was as high as 67 μM. (Wang M, 2020).

Favipiravir inhibits replication of seasonal influenza A and B viruses, including those resistant to adamantanes and NAIs, and avian A(H5N1), A(H7N9), viruses, at 50% effective inhibitory concentrations (EC_{50s}) of 0.03–0.94 μg/ml, 0.09–0.83 μg/ml, and 0.06–3.53 μg/ml, respectively. Combined treatment with oseltamivir and favipiravir resulted in 100% survival in mice infected

with an A(H5N1) virus and extended the treatment window to 96h post-infection. In a highly immunocompromised nude mouse model, prolonged therapy with favipiravir was more effective than NAIs in extending survival, but combination therapy with an NAI variably reduced lung viral titers and did not prevent the emergence of NAI-resistant variants (Hayden F, 2019).

In safety pharmacology studies, no effect on central nervous system (CNS) and respiratory systems were noted in rats up to 500 and 2000 mg/kg, respectively. In the in vitro hERG assay no meaningful effect on hERG current were noted up to 1000 μmol/L (157 μg/L). In telemetry study in male beagle dogs, no effects on blood pressure, heart rate, or electrocardiographic (ECG) parameters (PR, QRS, QT, QTc) were noted oral doses up to 150 mg/kg [Avigan Tablet 200 mg- Deliberation Results by PMDA, 2014].

Toxicity profile of favipiravir has been assessed in oral dose studies in rats and dogs (1 month) and oral dose study in monkeys (2 weeks). Major findings included effects on the hematopoietic tissues (decreases in erythrocyte-related parameters, associated with decreased myelopoiesis), effects on the liver (increases in alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin, increased liver weight, and vacuolization in hepatocytes), and testis toxicity. The AUC value in healthy adult Japanese male subjects treated with favipiravir in accordance with the proposed dosage regimen (oral administration of 1200 mg [first dose] and 400 mg [second dose] on Day 1, followed by 400 mg/dose BID from Day 2 to Day 5) was compared with the $AUC_{0\text{-}t}$ values obtained at the no observed adverse effect levels (NOAEL) (rats, 32 mg/kg/day; dogs, 10 mg/kg/day; monkeys, 100 mg/kg/day) in the oral dose studies. The AUC in humans was approximately 0.58 to 0.87 times that in rats, approximately 0.23 to 0.27 times that in dogs, and approximately 0.9 to 1.3 times that in monkeys, and the C_{max} in humans was approximately 0.75 to 0.87 times that in rats, approximately 0.21 to 0.24 times that in dogs, and approximately 2.1 to 2.2 times that in monkeys. In juvenile animals, favipiravir causes abnormalities in musculature and mortality during prolonged dosing (Hayden F, 2019). Favipiravir was non genotoxic in various in vitro and in vivo genotoxicity assays. No carcinogenicity studies have been conducted and it is not required as Favipiravir is indicated for a short period in clinical setting [Avigan Tablet 200 mg- Deliberation Results by PMDA, 2014].

The reproductive and developmental toxicity of favipiravir was evaluated in studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in mice, rats, and rabbits, and a rat study on pre- and postnatal development, including maternal function. The reproductive and developmental toxicity study data suggested that favipiravir may cause delayed development or death of embryos during the early stage of pregnancy, in which a pregnancy test may give a negative result in humans. Also, the teratogenicity of favipiravir was observed in all the animal species (4 species) assessed in embryo-fetal developmental studies; and the favipiravir exposure causing teratogenicity in animals is comparable to that in humans treated with favipiravir in accordance with the proposed dosage regimen. Thus, favipiravir has raised considerable concern about the teratogenic risk in humans [Avigan Tablet 200 mg- Deliberation Results by PMDA, 2014].

Based on the above reproductive and developmental toxicity data, favipiravir should be contraindicated for women who are pregnant or may possibly be pregnant, and women of childbearing potential and men whose partner is of childbearing potential should be advised to use contraception. Additionally, the precautionary statement about the early-embryo toxicity and teratogenicity of favipiravir should be included in the prescribing information [Avigan Tablet 200 mg- Deliberation Results by PMDA, 2014].

5.3. Clinical Experience

Favipiravir is a pyrazine derivative and a broad-spectrum antiviral drug approved in Japan for the treatment of novel influenza pandemics. Favipiravir is a pro-drug that is ribosylated and competes with purine nucleosides and interferes with viral replication by incorporation into the virus RNA and thus potentially inhibiting the RNA dependent RNA polymerase of RNA viruses. Favipiravir has a mechanism that prevents the propagation of RNA viruses, the drug is a reserve drug for pandemics associated with novel Influenza infections. It is also effective on a wide range of RNA viruses (including arenaviruses, phleboviruses, hantaviruses,flaviviruses, enteroviruses, respiratory syncytial virus, and noroviruses) including SARS CoV 2 and therefore is undergoing clinical evaluation in COVID-19 pandemic in many countries.

It is considered as a potential treatment option in Covid-19 and is undergoing several clinical trials to evaluate the safety and efficacy in Novel Corona Virus patients. Emergency approval of favipiravir (formulation: tablet, 0.2g) for a clinical trial in adult NCP patients (2020L00005) was announced by the National Medical Products Administration (NMDA) in China.

Two clinical studies conducted in China have been completed and published indicating efficacy of Favipiravir in COVID-19 patients. In one of the published studies conducted in China (Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial; https://doi.org/10.1101/2020.03.17.20037432) approximately 240 subjects were randomized and Favipiravir was compared against Umifenovir; Favipiravir can be considered as a preferred treatment because of its' higher 7 day's clinical recovery rate (71.43%) than Umifenovir (55.86%) and the time of cough relief and fever reduction of Favipiravir was significantly shorter than that of Umifenovir (Chen C, 2020). In another study; Favipiravir has shown to be superior to Lopinavir/Ritonavir in treatment of COVID-19 positive patients conducted in Wuhan, China. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that Favipiravir had more potent antiviral action than that of lopinavir/ritonavir. A shorter viral clearance time was found for the Favipiravir arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d, $P < 0.001$). The Favipiravir arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% versus 62.22% ($P = 0.004$). Multivariable Cox regression showed that Favipiravir was independently associated with faster viral clearance. No significant adverse reactions were noted in the Favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group (Cai Q, 2020). Many trials of Favipiravir are ongoing in which Favipiravir is evaluated in combination with Toclizumab or chloroquine or alone against Placebo and trials are ongoing in USA, EU and Japan in patients of mild Covid and moderate Covid 19.

The safety profile of Favipiravir is well established and no additional unexpected safety events are anticipated. In Japanese clinical studies and the global phase III study (studies conducted with dose levels lower than the approved dosage), adverse reactions were observed in 100 of 501 subjects (19.96%) evaluated for the safety (including abnormal laboratory test values). Major adverse reactions included increase of blood uric acid level in 24 subjects (4.79%), diarrhoea in 24 subjects (4.79%), decrease of neutrophil count in 9 subjects (1.80%), increase of AST (GOT) in 9 subjects (1.80%), increase of ALT (GPT) in 8 subjects (1.60%).

Early embryonic deaths and teratogenicity have been observed in pre-clinical studies hence favipiravir is not to be administered to women known or suspected to be pregnant. When administering favipiravir to women of child-bearing potential a pregnancy test is to be performed as it is absolutely contraindicated in pregnancy. Effective contraceptive methods during and for 7 days after the end of the treatment have to be instructed to male patients being administered the drug.

Completed trials in COVID-19

Title	Dose and duration	Patient population	Result
Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study (Q. Q. Cai, M. Yang, D. Liu et al., Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, Engineering, https://doi.org/10.1016/j.eng.2020.03.007	FPV (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) Interferon α 5 million Units twice a day. Max. 14 days	**Excluded**: severe clinical condition (meeting one of the following criteria: a RR greater than 30 per minute, oxygen saturation below 93%, oxygenation index (OI) <300 mmHg, respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment)	Mean viral clearance time 4 days versus 11 days with Lopinavir/Ritonavir) CT p<0.001 Significant improvement in chest clearance 91.43 % versus 62.22 p<0.004 Adverse events 11.43% vs 55.56% Diarrhoea, LFT increase, Anorexia
Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial (https://doi.org/10.1101/2020.03.17.20037432.) N=240	FPV (Day 1: 1600 mg twice daily; Days 2–7/10: 600 mg twice daily) . Max. 10 days	diagnosed as COVID-19 pneumonia; **Excluded**: critical patients whose expected survival time < 48 hours;	7 day's clinical recovery rate: 55.86 % in the arbidol group and 71.43% in the favipriravir arm

Ongoing trials in COVID-19

Title	Dose and duration	Patient population	Result
Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019 (https://clinicaltrials.gov/ct2/show/NCT04310228) N= 150 (3:1:1)	FPV (Day 1: 1600 mg twice daily; Days 2–7: 600 mg twice daily. Max. 7 days	Included: Clinically diagnosed with Corona Virus Disease 2019 ; Increased interleukin-6 Excluded: severe clinical condition (meeting one of the following criteria: a RR greater than 30 per minute, oxygen saturation below 93%, oxygenation index (OI) <300 mmHg, respiratory failure, shock, and/or combined failure of	Ongoing

		other organs that required ICU monitoring and treatment); Predicted clinically that there is no hope of survival, or cases of deep coma that do not respond to supportive treatment measures within three hours of admission	
Double-blind, placebo controlled, multicenter study that evaluates the performance and safety of the Favipiravir combined with supportive care for adult patients with COVID-19-moderate type. N= 100 (1:1)	Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days. (adverse event related to liver injury of grade≥3 (NCI CTCAE v5.0), the dose is to be reduced to 600mg BID; discontinued from treatment if he/she re-experiences any adverse event related to liver injury of grade≥3 after dose reduction)	Included: Chest imaging (CT as first option or X-ray if CT not possible)-documented pneumonia; pyrexia or either respiratory rate >24/min and <30/min or cough; Excluded: Refractory nausea, vomiting, or chronic gastrointestinal disorders. Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN; Gout/history of gout or hyperuricemia (above the ULN); Oxygen saturation (SPO2)≤93% or arterial oxygen partial pressure (PaO2)/ fraction of inspired O2 (FiO2)≤300 mmHg;	Ongoing
Phase 3 Clinical Study of Favipiravir in Patients with COVID-19 Non-Severe Pneumonia (https://rctportal.niph.go.jp/en/detail?trial_id=JapicCTI-205238) N=96	Oral Multiple Dose	Included: confirmed infection with SARS-CoV-2. Lung involvement confirmed with chest imaging, Patients with fever of 37.5 degrees Celsius or more. Excluded: Ten days or more have passed	Ongoing

		since the fever (37.5 degrees Celsius or more) started. Patients with severe hepatic or renal impairment	
Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia (https://clinicaltrials.gov/ct2/show/NCT04319900) N=150	FPV (Day 1: 1600 mg twice daily; Days 2–10: 600 mg twice daily) Max. 10 days	Included: (1) No apparent absorption or progression of chest radiograph was observed within 7 days; (2) respiratory symptoms (chest tightness, or cough, or breathing difficulties); Excluded: Clinical prognostic non-survival, palliative care, or in deep coma and no have response to supportive treatment within three hours of admission	Ongoing
A Phase 2 Randomized, Open Label Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild COVID-19 (https://clinicaltrials.gov/ct2/show/NCT04346628?cond=mild+covid&draw=2&rank=4) N=120	Favipiravir administered orally, 1800 mg on the first dose (day 1) followed by 800 mg twice daily for the next 9 days (days 2-10).	Included: Patients with laboratory confirmation of infection with SARS-CoV-2 and who are PCR positive (within five days or fewer prior to enrollment) Asymptomatic or mild respiratory disease, No more than four of the following of mild severity, and no more than two of moderate severity: Cough, Sore throat, Headache, Nasal congestion, Body aches and pains Fatigue. Excluded: Concomitant bacterial respiratory infection History of abnormalities of uric acid metabolism. Renal insufficiency requiring hemodialysis or continuous	Ongoing

		ambulatory peritoneal dialysis (CAPD). Liver impairment greater than Child Pugh 1. Psychiatric disease that is not well controlled (controlled defined as stable on a regimen for more than one year)	

Favipiravir is already approved in Japan since 2014 (Avigan Tablets, Toyama Chemical Co., Ltd.), for the treatment of the new or re-emerging pandemic influenza virus infections. Favipiravir was also approved for treatment of novel influenza on February 15, 2020 in China . It is a reserve drug stockpiled for novel pandemics and is currently being considered as a treatment option in COVID-19.

5.4. Benefit-Risk Assessment

Coronavirus disease 2019 (COVID-19) pandemic outbreak is currently ongoing in India and most part of the World, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of April 19, 2020, there have been 2.3 million reported cases worldwide. Importantly as of April 19, 2020, India reported total confirmed cases of 15,712 with 507 fatalities as per data of Ministry of Health, Govt of India.

Numerous antiviral agents, immunotherapies, and vaccines are being investigated as potential therapies, however, so far, none have been approved for COVID-19 and hence there is no specific/ approved treatment for COVID-19 anywhere in the world. Therefore, it is urgently necessary to have effective antiviral agent/s to combat the disease.

Favipiravir is a drug approved for novel Influenza pandemics. It has a mechanism that prevents the propagation of RNA viruses, the drug has antiviral effect on novel coronavirus which is classified into the same type (single-stranded RNA virus) of influenza virus. Favipiravir has shown good efficacy in two clinical trials against COVID-19. Many trials are currently ongoing in US; Europe and Japan to evaluate the efficacy of favipiravir in mild and moderate COVID-19 based on its antiviral properties; in-vitro activity against SARS-CoV-2 and signal of efficacy in clinical studies. The safety and tolerability of favipiravir were well established, although some data regarding the potential teratogenicity of FP were collected in all animal species assessed.

Warnings in the Avigan labeling include that favipiravir is contraindicated in women who might be or are pregnant and in lactating women because of its association with embryonic deaths and teratogenicity in animal studies. Favipiravir has been reasonably well tolerated in clinical studies, although it is associated with dose-related, asymptomatic increases in serum uric acid levels and should be used with care in patients with gout or a history of gout and in those with hyperuricemia. Other adverse events may include mild to moderate diarrhea, asymptomatic increase of transaminases, and uncommonly decreased neutrophil counts (Hayden F, 2019).

The definite role of Favipiravir in the treatment of COVID-19 is emerging and clinical evidence generated in favor of favipiravir makes it a potential treatment option in the current COVID-19

pandemic that has caused extensive mortality and morbidity globally. Favipiravir is a potential treatment option in COVID-19 and must be evaluated in Indian subjects against COVID-19. The evidence supports benefit of favipiravir therapy over the risks involved in patients with COVID-19. Hence, Glenmark proposes to conduct a randomized, multi-center, open-label trial in Indian patients comparing favipiravir tablets to be administered twice daily with standard supportive care compared to standard supportive care alone mild to moderate COVID-19.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

- The primary objective of this study is to evaluate the clinical efficacy of favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

6.2. Secondary Objectives

- The secondary objective is to evaluate the safety and tolerability of favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a phase 3, randomized, multi-center, open-label, clinical study evaluating the efficacy and safety of favipiravir with standard supportive care vs standard supportive care alone in the treatment of patients with mild to moderate COVID-19. It is a parallel arm study in which eligible patients will be randomized into 2 groups: one group will receive favipiravir along with standard supportive care and the control group will receive the standard supportive care as per the standard treatment guideline for COVID-19. A total of 150 male and female subjects will be randomized in a 1:1 ratio to 1 of 2 treatment arms. 90 subjects with mild COVID-19 and 60 subjects of moderate COVID-19 will be randomized in the study. All the protocol related procedures will be conducted after obtaining valid written informed consent from the subject. Patients with a confirmed diagnosis of COVID-19 (based on RT-PCR) will be included in the study. Subjects qualifying screening criteria and enter an evaluation period. The study will include a screening period (Day -3 to Day 0), followed by an evaluation period where the patients with mild to moderate COVID-19 will be administered treatment for a maximum of 14 days. The total duration of study participation will be a maximum of 28 days from the day of randomization.

The study consists of the following periods as described below:

Screening (Day -3 to Day 0): During which the screening assessments will be performed.
Baseline (Day 1): On Day 1 randomization will occur.
Treatment Period (Day 1 to maximum Day 14)
Treatment (favipiravir along with standard supportive care or standard supportive care only) will be administered BID for a maximum of 14 days.
Day of Discharge from the treatment will occur based RT- PCR negative.

The total duration of study participation will be a maximum of 28 days from randomization for each subject.

Eligible subjects will be randomized to receive one of the following treatments:

Arm 1: Favipiravir tablets; 3,600 mg (1,800 mg BID) (Day 1) + 1,600 mg (800 mg BID) (Day 2 onwards) for up to maximum of 14 days, along with standard supportive care.

Arm 2: Standard supportive care alone.

Balanced and stratified randomization will be planned in the Arm 1 and Arm 2 based on baseline disease severity.

See Table 2 for the Schedule of Assessments.

Each subject will undergo screening assessments at Screening (Day -3 to Day 0). At baseline and during the study, standard supportive care will be provided to all subjects in accordance with latest guidelines issued by Ministry of Health and family welfare; Government of India.
At Screening (Day -3 to Day 0), informed consent and protocol eligibility will be established. Written informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments.
After informed consent is obtained, subjects will be evaluated for eligibility based on the inclusion and exclusion criteria (see Section 8), which will require review of medical history and concomitant medications, vital signs, clinical examination, 12-lead electrocardiogram (ECG, chest

X-ray/CT scan lung, SpO2, clinical laboratory evaluations (hematology, blood chemistry, urinalysis), serum pregnancy testing for female subjects of child bearing potential. Adverse event (AE) monitoring will begin after informed consent is obtained. Randomization will occur on Day 1 of the study. Study treatment will be administered in patients with mild to moderate COVID-19 for a maximum of 14 days. Subject clinical assessment will be performed daily and recorded in the CRF and other protocol specific procedures will be done as per Schedule of assessments (Table 2).

The endpoints to be measured in this study are described in Section 14.3. Subjects will be in-house for 14 days or more if required as per PI judgment.

The end of the study will be the date of the hospital discharge/ maximum 28 days of hospitalization (whichever is earlier) for the last randomized subject in the study.

7.1.1. Rationale for Study Design, Dose(s) and Comparator(s)

The study design is randomized; open-label parallel group in which subjects with mild to moderate COVID-19 will be stratified based on disease severity and randomized equally in a ratio of 1:1 in two groups; favipiravir and standard supportive care will be provided in the experimental group while the control group will receive standard supportive care only.

The open-label study design will not introduce bias as the end-point to be measured are objective in nature and designing a double-blind study in the time of pandemic may delay the evaluation of a potential treatment of a rapidly increasing pandemic.

Dosage selected for the study is based on dosage recommended in Guidance of antiviral drug treatment for COVID-19 1st edition; (26 Feb. 2020); The Japanese Association for Infectious Diseases. Same dose is also currently under evaluation in the US trial in mild COVID-19 patients. (Ref: Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild COVID-19; ClinicalTrials.gov Identifier: NCT04346628). The dosage has already been evaluated in Influenza indication globally and does not possess any additional safety concern.

Since there is no specific antiviral therapy currently approved for COVID-19; the comparator arm is chosen as best standard supportive care as per the guidance issued by ICMR.

On 22 March 2020, Italy has approved favipiravir for experimental use against COVID-19 and has begun conducting trials in 3 regions most affected by the disease. Multiple trials are ongoing in USA and in Japan in mild to moderate Covid-19.

The proposed phase 3 clinical study will help to provide evidence regarding efficacy and safety of favipiravir combined with standard supportive care in the treatment of COVID-19 and will help to address the unmet medical need in the current pandemic in the most timely manner.

7.1.2. Estimated Duration of Subject Participation

150 subjects with mild to moderate COVID-19 will be enrolled (randomized) in the study in 1:1 ratio to favipiravir with standard supportive care or standard supportive care. 90 subjects with mild COVID-19 and 60 subjects of moderate COVID-19 will be randomized in the study.

The anticipated maximum total study duration for each subject is a maximum of 28 days from randomization. This will consist of the baseline, the treatment period of up to 14 days, and the day of discharge from the treatment on day 14 or more as per PI assessment.

7.2. Treatment Assignment

Subjects will be assigned to stratified randomized treatments based on a computer-generated randomization scheme which will be done centrally. The randomization scheme and identification for each subject will be included in the final clinical study report for this study

7.3. Dose Adjustment Criteria

Not applicable.

7.4. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The Institutional Review Board (IRB)/independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

7.5. End of the Study

The end of the study (study completion) is defined as the date of the last protocol-specified assessment (including telephone contact) for the last subject in the study.

Table 2: Schedule of Assessments

Study Period	**Screening**	**Baseline**	**Evaluation Period**		
Time Point	**Day -3 to Day 0**	**Day 1**	**Day 2 to Day 14**	**Day 15 to Day 28**	**Day of Discharge[##]**
Informed Consent	√				
Demographics	√				
Review Inclusion/Exclusion Criteria	√	√			
Randomization		√			
Medical history	√				
SARS CoV2 RT- PCR	√		√	√	√
Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)*	√	√	√	√	√
Vital parameters (Body temp**, RR, BP, Pulse), Body weight*	√	√	√	√	√
Complete Physical Examination	√	√	√	√	√
Height	√				
Prior and concomitant medication	√	√	√	√	√

Study Period	**Screening**	**Baseline**	**Evaluation Period**		
Time Point	**Day -3 to Day 0**	**Day 1**	**Day 2 to Day 14**	**Day 15 to Day 28**	**Day of Discharge[##]**
SpO_2	√	√	√	√	√
CXR/CT scan lung[1]	√				
Check for Oxygen support/NIV/MV/ECMO support		√	√	√	
ECG	√				
Laboratory parameters	√		#	#	√
Serum Pregnancy test[2]	√				
Efficacy assessment*		√	√	√	√
Safety assessment	√	√	√	√	√
Administration of Study medication		√	√		

*Clinical examination, vitals and other patient care procedures will be done as per treating Physician. Clinical symptoms and Vital parameters will be assessed twice daily, morning and evening on day 1 to day 28.

**Axillary temperature will be taken, if not measured temperature at other sites will be taken.

Patient care requirement beyond Day 14 will be as per investigator judgment.

[1]Documented pneumonia based on Chest X-ray/CT scan lung within 3 days prior to randomization.

[2]Female subjects of child bearing potential only, Serum β-HCG at screening.

Lab tests can be repeated as per standard management for COVID-19

[##]Day of Discharge from the treatment will occur based RT- PCR negative, clinical cure . The subject will be discharged from study only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative.
Note: Recovery status check – If patient is getting recovered in less time and discharged that does not mean discontinued.
Additional procedures can be performed as per standard management for COVID-19.
All the assessments for Premature discontinuation will be considered on the Day of discharge. Both the recovered subjects and Premature discontinued subjects will be perform assessments on Day of Discharge.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Voluntarily participating in the clinical study; fully understanding and being fully informed of the study and having signed the Informed Consent Form (ICF); willingness and capability to complete all the study procedures
2. Age 18-75 years (inclusive) at the time of signing ICF
3. Patients with laboratory confirmation of infection with SARS-CoV-2 by positive RT-PCR (within 48 hours prior to randomization)
4. For female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pretreatment serum or urine pregnancy test
5. Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment;
6. Not participating in any other interventional drug clinical studies before completion of the present study.

Additional Inclusion criteria for mild cases only:

7. Time interval between symptoms onset and randomization to no more than 7 days
8. Pyrexia (temperature < 102.2^{o}F); respiratory rate 12 to ≤20/min.
9. No more than four of the following of mild severity, and no more than two of moderate severity (Mild is defined as symptoms not requiring any or minimal therapeutic intervention; moderate is defined as symptoms which produce small impairment of function and require some form of therapeutic intervention; severe is defined as symptoms resulting in marked impairment of function):
    - Cough
    - Sore throat
    - Headache
    - Nasal congestion
    - Body aches and pains
    - Fatigue

Additional Inclusion criteria for moderate cases:

10. Patients with the interval between symptoms onset and randomization is no more than 10 days
11. Chest imaging (CT as first option or X-ray if CT not possible)-documented pneumonia
12. Patients with pyrexia (axillary ≥98.6^{o}F or oral ≥99.5^{o}F); respiratory rate >20 to <30/min

8.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Where, in the opinion of the investigator, participation in this study will not be in the best interest of the subject, or any other circumstances that prevent the subject from participating in the study safely.
2. Severe infection, defined as need for invasive or non-invasive ventilator support, ECMO or shock requiring vasopressor support.
3. Inability to intake or tolerate oral medications.
4. Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN
5. Gout/history of gout or hyperuricemia (above the ULN)
6. Prolonged QT, defined as QTcF ≥450 milliseconds for men and as QTcF ≥470 for women
7. Known severely reduced LV function (Ejection fraction <30%)
8. Oxygen saturation (SPO2)≤93% or arterial oxygen partial pressure (PaO2)/ fraction of inspired O2 (FiO2)≤300 mmHg;
9. Requires ICU care for management of ongoing clinical status.
10. Known allergy or hypersensitivity to Favipiravir;
11. Known severe renal impairment [creatinine clearance (CrCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis;
12. Asthma or chronic obstructive lung disease
13. Psychiatric disease that is not well controlled (controlled defined as stable on a regimen for more than one year).
14. Pregnant or lactating women;
15. Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug.
16. Clinical prognostic non-survival, palliative care, and have no response to supportive treatment within three hours of admission

8.3. Subject Withdrawal Criteria

A subject may voluntarily discontinue study participation at any time after giving informed consent and before the completion of the study. Subjects may also be withdrawn from study drug treatment at the discretion of the Investigator or Sponsor for safety, noncompliance, or administrative reasons. The Investigator may also discontinue the subject's study participation at any time at his/her discretion and for any reason.

The reasons for subject withdrawal will be recorded and may include, but are not limited to:

1. Withdrawal of consent by the subject to continue in the study. If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.

2. Development of a serious or intolerable adverse event (AE) that necessitates discontinuation at the discretion of the Investigator (the AE section of the CRF/electronic case report form (eCRF) must be completed; AE includes serious adverse event (SAE) and death.
3. At the discretion of the Investigator, when he/she believes continued participation is not in the best interest of the subject.
4. As per discretion of Investigator, where the clinical condition of the patient worsens
5. At the discretion of the Investigator, when the subject does not adhere to the study procedures.
6. A protocol deviation that, in the opinion of the Sponsor and Investigator, warrants discontinuation from the study.
7. The Investigator withdrew the subject from the study if the subject suffered from significant inter-current illness during the course of the study.
8. Positive pregnancy test at any time in the study.

Any subject withdrawal during the study along with the reason was documented.

Discontinued subjects were not replaced. In case of premature discontinuation, the reason and cause was documented. The Investigator (or designee) documented the reason for withdrawal in the eCRF. All follow-up assessments were conducted at the early withdrawal. Subjects discontinued from the study at any stage were considered for safety analysis. Discontinued subjects will not be replaced.

Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), drug safety problems, or at the discretion of Glenmark. In addition, Glenmark retains the right to discontinue development of favipiravir at any time.

If a study is prematurely terminated or discontinued, Glenmark will promptly notify the Investigator, ethics committee and regulatory authority. After notification, the Investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a time period set by Glenmark. As directed by Glenmark, all study materials must be collected and all eCRFs completed to the greatest extent possible.

8.3.1. Lost to Follow-up

A subject will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status on discharge. Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol.

8.3.2. Permanent Discontinuation of Study Drug

A subject who is permanently discontinued from further receipt of study drug, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 9.5).

8.3.3. Replacement of Subjects

Discontinued subjects will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

The following study drugs will be supplied by Glenmark for the study:

Study Drugs

Investigational Product:

Name of Investigational Product: Favipiravir 200 mg tablets plus Standard supportive care
Dosage Form: Tablet
Dose: Favipiravir 3,600 mg (1,800 mg bid) (Day 1) + 1,600 mg (800 mg bid) (Day 2 or later) for up to a maximum of14 days.
Dosage Frequency: Twice daily.
Mode of Administration: Twice daily with food preferably at similar time of the day
Route of Administration: Oral
Manufacturer: Glenmark Pharmaceuticals Ltd.

Comparator
Name of Comparator: Standard supportive care.

Administration
The Investigational product will be dispensed at as per the schedule of assessments (Table 2). The subjects will be instructed to take the study medication as described.

9.2. Concomitant Medications

9.2.1. Prior Medications

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication eCRF or Concomitant Non-drug treatment eCRF. The Investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the Investigator will record the medical condition on the Medical History eCRF.

9.2.2. Permitted Concomitant Medications

Permitted concomitant Medications:
Medications (that are not prohibited by the protocol) for medical conditions other than COVID-19 at the time of baseline should be continued throughout the study in the same dose. A change of dose in concomitant medications is permitted provided it is safe for the patient to continue in the study. The adverse event leading to change of dose of concomitant medication must be documented.
The Investigator should be informed as soon as possible about any medication taken from the time of baseline until the end of the clinical phase of the study. Any medication taken will be fully documented in the CRF.

9.2.3. Prohibited Concomitant Medications

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Hydroxychloroquine or chloroquine	Dizziness, nausea	QTc prolongation, heart block.
Pyrazinamide	Blood uric acid level increases. When pyrazinamide 1.5g once daily and favipiravir 1200 mg /400 mg BID were administered, the blood uric acid level was 11.6 mg/dL when pyrazinamide was administered alone, and 13.9 mg/dL in combination with favipiravir.	Reabsorption of uric acid in the renal tubule is additively enhanced.
Repaglinide	Blood level of repaglinide may increase, and adverse reactions to repaglinide may occur.	Inhibition of CYP2C8 increases blood level of repaglinide.
Theophylline	Blood level of favipiravir may increase, and adverse reactions to favipiravir occur.	Interaction with XO may increase blood level of favipiravir
Famciclovir Sulindac	Efficacy of these drugs may be reduced.	Inhibition of AO by favipiravir may decrease blood level of active forms of these drugs.

9.2.4. Lifestyle and/or Dietary Restrictions

- Women of child-bearing potential must immediately contact the Investigator if they suspect they might be pregnant and if they have changed, or plan to change their birth control method or collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study.

9.3. Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during remote / on site monitoring visits and at the completion of the study.

The administration of study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. Site need to keep accountability of all used and unused investigational product.

See Section 10 for additional information on study drug supplies.

9.4. Randomization

9.4.1. Allocation to Treatment Groups

Subjects will be assigned to stratified randomized treatments based on a computer-generated randomization scheme which will be done centrally. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

9.5. Subject Completion

Treatment duration is a maximum of 14 days and the total study duration will be maximum for 28 days from randomization. All the subjects will be hospitalized as per current standard of treatment and will be discharged only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative. The Day of Discharge from the treatment will occur based RT- PCR negative, clinical cure.

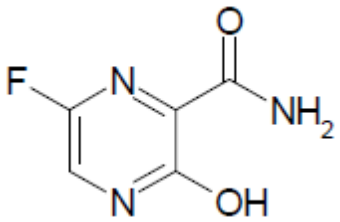
10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Investigational Product

Investigational Product: Favipiravir 200 mg tablets and standard supportive care

Chemical Name and Structural Formula of Favipiravir 200 mg tablets
Chemical name: 6-Fluoro-3-hydroxypyrazine-2-carboxamide
Structure formula:



Molecular formula: C5H4FN3O2
Molecular weight: 157.10
Description: Favipiravir is a white–light yellow powder. It is sparingly soluble in acetonitrile and methanol, slightly soluble in water and ethanol (99.5).
Melting point: 187–193ºC

Comparator: Standard supportive care.

10.2. Study Drug Packaging and Labeling

The Investigational Product will be packed separately. Each pack will contain appropriate number of tablets of study drug (Favipiravir). Each subject kit will comprise of appropriate number of containers containing sufficient study drug for the entire duration in the study as planned. Subject kit will contain same type of containers labelled with colour labels.

Subjects randomized to the test group will be allocated individual subject pack according to the randomization number and from individual subject pack containers will be dispensed as per study schedule.

The individual subject pack containing label will minimum be labelled with the following information:

1. Protocol Number
1. Name of the Test Drug
2. Pharmaceutical dosage form, Route of Administration, Quantity of dosage units
3. Instructions for Administration of the Medication
4. Trial subject identification number/treatment number

5. "For Clinical Trial Use Only"
6. Storage Conditions
7. "Keep out of reach of children"
8. Batch Number and Expiry Date
9. Details of Sponsor and Investigator

The Study Monitor should be notified immediately of details of any supplies, which are inadvertently damaged. Details of any supplies, which are inadvertently damaged or unaccountable, for any reason, will be documented on Drug Accountability log that will be collected by the Study monitor at the end of the Study.

At the end of the Study, it must be possible to reconcile delivery records with those of used and unused stocks. Account will be given of any discrepancies.

Procedure for Handling of Unused Investigational Product

The study drug which included Test drug will be provided by Glenmark Pharmaceuticals Limited. The dispensation of the Investigational Drug for every subjects will be performed and recorded. Used containers returned with remaining tablets by the subjects will collected. In case any unused investigational product is returned by the subjects, appropriate records will be maintained. These records will tally with the supplies initially sent to the investigational site. At any time the figures of supplied, used and remaining investigational product will match. The remaining Investigational Product both unused and used containers will be returned to Glenmark Pharmaceuticals Limited at the end of the trial, in accordance with the study monitor's instructions.

10.3. Study Drug Storage

Investigational product (IP) should be stored in a dry place, at a room temperature between 15°C to 30°C. The Principal Investigator (or designee) is responsible for IP accountability at the site and its documentation. The Principal Investigator must also ensure that the dispensing and recording of IP is done only by authorized personnel. The IP records must be readily available for inspection by the study monitor and/or auditor/regulatory agency personnel. No medication (new or used) can be returned to the Sponsor or disposed of at the investigational site until the Sponsor's clinical monitor has verified/reconciled the accuracy of the study medication records at the site and indicated whether the medication should be destroyed at the site or returned to the Sponsor. The study monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

10.4. Study Drug Accountability

The Investigator (or designee) is responsible for study drug accountability and its documentation at the site. The Investigator must also ensure that the dispensing and recording of study drug is done only by authorized personnel. The study drug records must be readily available for inspection by the Study Monitor and/or auditor/regulatory agency personnel. Upon completion of the study, copies of 'study drug accountability records' will be returned to the Sponsor or its designee. Refer to the Investigational Product Manual or other written instructions provided by the Sponsor or its designee for contact information and specific shipping and return instructions.

10.5. Study Drug Handling and Disposal

No study drug (used or unused) can be returned to the Sponsor or disposed of at the investigational site until the Sponsor's Study Monitor has verified/reconciled the accuracy of the study medication records at the site or through remote monitoring and indicated whether the medication should be destroyed at the site or returned to the Sponsor. The Study Monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

11. ASSESSMENT OF EFFICACY

Detailed statistical methods will be provided in the Statistical Analysis Plan (SAP).

Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days]
The time until cessation of oral shedding of SARS-CoV-2 virus with a time frame of up to 28 days is the primary assessment. It is the time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab.
The sample collection will take place as described in the Schedule of Assessments (Table 2). The throat and nasal swab in viral transport media (VTM) and transported on ice. The sample collection and SARS-CoV2 RT-PCR test will be described in the Laboratory manual

Time from randomization to clinical cure based on clinician assessment
The clinical cure is the recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours) defined as (axillary temperature ≤ 97.8°C; respiratory frequency ≤ 20 times/min; Oxygen saturation ≥ 98% without oxygen inhalation; mild or no cough). These are for those patients which presented with clinical signs and symptoms at baseline. The clinical symptoms will be assessed as described in the Schedule of Assessments (Table 2).

Rate of Clinical cure at day 4/7/10/14
The proportion of subjects with clinical cure will be evaluated at day 4, 7, day 10 and day 14 from randomization in the study. The clinical cure is the recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours) defined as (axillary temperature ≤ 36.6 °C; respiratory frequency ≤ 24 times/min; Oxygen saturation ≥ 98% without oxygen inhalation; mild or no cough). The clinical symptoms will be assessed as described in the Schedule of Assessments (Table 2).

Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14

The proportion of subjects with SARS-CoV2 RT-PCR test negative in upper respiratory tract specimen will be evaluated at day 4, 7, day 10 and day 14 from randomization in the study. The SARS-CoV2 RT-PCR test will be assessed as described in the Schedule of Assessments (Table 2).

Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation.
The time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation will be evaluated.

Time from randomization to hospital discharge

The Time from randomization to hospital discharge will be evaluated.

All the end points will be evaluated from randomization until the date of hospital discharge or day 28, whichever is earlier.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in the Schedule of Assessments (Table 2)

Stopping/discontinuation/withdrawal criteria are listed in Section 7.4 and Section 8.3.

In case of premature discontinuation, the reason and their cause must be documented. All appropriate assessments should be conducted at the early withdrawal. If the withdrawal is due to an AE, the AE should be monitored until it is resolved or it has returned to a status that was prior to the AE or subject is not reachable or subject is not willing to provide information or up to 3 months from last study contact, whichever happens earlier.

12.1.1. Demographic/Medical History

Subject demography information will be collected at the Screening. Demography information includes date of birth (or age), sex, race etc.

Medical History and Physical Examinations

Medical and surgical history and current medical conditions will be recorded at the Screening. All relevant medical and surgical history within 5 years must be noted in the Medical History eCRF.

Physical examinations (comprehensive or symptom directed) will be performed as designated on the Schedule of Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening will be recorded on the Medical History eCRF.

A complete physical examination should include general appearance, head, neck, face, eyes, ears, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, lymph nodes, nervous system, skin, and musculoskeletal system.

Screening data will be collected at the Screening, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline. Changes from baseline physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

12.1.2. Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure, respiratory rate, body temperature and pulse) will be obtained as designated on the Schedule of Assessments (Table 2).

One pulse measurement will be taken after the subject has been sitting and resting for at least 5 minutes and before blood samples are taken. The pulse measurement will be followed by BP measurement. BP readings should be taken while the subject is in a comfortable position with the arm supported at the level of the heart. Ideally, seated BP should be measured of the same arm, with the same machine. A standard mercury sphygmomanometer with a standardized cuff adapted to the size of the subject's arm is recommended.

12.1.3. Weight and Height

Height be collected at the screening and weight according to the Schedule of Assessments (Table 2), where weight is measured in kg and height in meters).

12.1.4. Physical Examination

Physical examinations (comprehensive or symptom directed) will be performed as designated on the Schedule of Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening will be recorded on the Medical History eCRF.

A complete physical examination should include general appearance, head, neck, face, eyes, ears, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, lymph nodes, nervous system, skin, and musculoskeletal system. The subject should always be evaluated for the presence of edema.

Baseline data will be collected at the Baseline, and new findings discovered on subsequent physical examinations should be recorded as changes from baseline. Changes from baseline physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

12.1.5. Electrocardiogram

A 12-lead ECG will be taken at Screening after the subject has been lying down resting. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality and provide assessment related to clinical significance.

12.1.6. Laboratory Assessments

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Appendix 2.

Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures and Assessments (Table 2) shows that blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

A local laboratory should usually be used to measure laboratory parameters that are to be assessed as part of the safety analyses for the electronic clinical study report (CSR).

The following tests will be performed:

1. SARS CoV2 RT-PCR
2. Complete Blood Count (CBC) comprising of Hemoglobin, Hematocrit (PCV), Red Blood Cells (RBC), White Blood Cells (WBC), Platelets and Differential Blood Cell Counts (Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils)
3. Biochemistry comprising of Glucose (fasting and post-prandial), plasma total protein, albumin, serum creatinine, serum lactic acid, bilirubin (total, direct), ALT, AST, ALP, GGT, Na, K, Cl,

bicarbonate, magnesium, phosphorus, calcium, alkaline phosphatase, uric acid, C-reactive protein.

4. Urinalysis comprising of Color, pH, Protein, Glucose, Ketone, Nitrite/Leukocyte esterase and Microscopic examination, Urine culture (only in patients suspected or known to have urinary tract infection)
5. A serum pregnancy test will be done for women of childbearing potential. A Serum β-HCG at screening will be done. In the event of suspected pregnancy during the study the test should be repeated and if pregnant, the subject should be discontinued and followed up as per Pregnancy Report Form provided.

(Note of any other test can be performed based on Investigator discretion/patient safety).

12.1.7. SpO2

SpO2 reading which indicates percentage of blood oxygen saturation and will be measured as mentioned in the Schedule of assessments (Table 2).

12.2. Adverse and Serious Adverse Events

The Investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

The reference safety information for favipiravir prescribing information (PI) is in Appendix 3.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of the study drug, whether or not related to the study drug. An AE includes any event, regardless of the presumed causality between the event and the study drug.

Events that, while not necessarily meeting the definition of AEs, should be treated as such because they may be reportable to Regulatory Authorities according to AE reporting regulations, whether or not considered causally associated with investigational product, include the following:

- Study drug overdose, whether accidental or intentional
- Study drug abuse
- An event occurring from study drug withdrawal
- Any failure of expected pharmacological action
- Inadvertent or accidental study drug exposure (eg, product leaking or being spilled onto a subject or care-giver)

- Unexpected therapeutic or clinical benefit from the study drug
- Medication errors (ie, incorrect route of administration, incorrect dosage, use of incorrect product).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Note that significant worsening of symptoms (ie, requiring systemic steroids, antibiotics, or hospitalization will be reported as an AE.

12.2.1.2. Assessment of Severity of Adverse Events

As routine practice, subjects with mild and moderate COVID-19 are admitted in the hospital. Since, already hospitalized subjects will be enrolled in the study, initial hospitalization will not be considered as SAE. However, extension of hospitalization will be considered as SAE.

The severity of AEs will be classified according to the Common Terminology Criteria for Adverse Events, CTCAE v5.0 (Link to CTCAE V5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

The criteria for assessing severity are different from those used for seriousness (see Section 12.2.1.3 for the definition of an SAE).

The Reference Safety Information for favipiravir (Avigan Tables 200 mg) will be the Prescribing Information sections on Warnings, Precautions, Contraindications and Adverse Reactions.

12.2.1.3. Serious Adverse Event

A SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization

  - NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in disability/incapacity
  - NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The severity of AEs is classified according to the CTCAE v5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

12.3. Relationship to Study Drug

The relationship of AEs to study medication is classified as follows:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment

- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

For each AE, the Investigator should answer the following question with Yes or No:

- Was there a reasonable possibility (evidence) that the drug caused the AE?
  - A reasonable possibility means that there are facts (evidence) or arguments to suggest a causal relationship.
  - NOTE: For subjects that have not started receiving study medication, or run-in phase medications, the answer must be no.

12.4. Recording Adverse Events

12.4.1. Collection of Adverse Events

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of signing the informed consent form (ICF) until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (eg, study drug, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication that is a Glenmark product, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to the Sponsor within 24 hours, as indicated in Section 12.5.

The Investigator will enquire about the occurrence of AEs/SAEs at throughout the study (including Early Withdrawal and where applicable), by asking the following non-leading verbal question of the subject (or care-giver, where appropriate):

- “Have you had any medical problems since last meeting?”

All AEs not resolved by the end of the study or that have not resolved upon the subject’s discontinuation in the study must be followed until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

12.4.2. Recording of Adverse Events

All AEs, regardless of the seriousness, severity or relationship to the study medication must be recorded on the AE CRF.

Adverse events that meet the definition of a SAE must be reported on the SAE Form provided for this study.

Adverse events must be documented in clear, unambiguous medical language. Do not use abbreviations or acronyms.

For each AE record only the diagnosis, do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available record each sign and symptom as an AE, when a diagnosis becomes available, update the AE CRF, to record the relevant diagnosis only.

In general abnormal findings at screening should be recorded in the subject's Medical History or in the Concurrent Conditions section in the CRF. However if, in the Investigators opinion, the finding is clinically significant and represents a condition that was not present at signing of informed consent, then the finding must be reported as an AE.

12.5. Reporting Adverse Events

Prompt notification of SAEs by the Investigator to Glenmark is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Glenmark has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Glenmark will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigators.

All SAEs must be reported to the Sponsor immediately or within 24 hours of the Investigator or their staff becoming aware of them. Reporting should be performed by recording as much information as is available at the time on the SAE Form and sending it to the contact information provided below:

Fax: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information. Follow-up reports must be submitted to the Sponsor until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

Additional information will be requested by the Sponsor as necessary.

12.5.1. Pregnancy

The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 2 weeks of

learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy form, immediately or within 24 hours of the Investigator learning of its occurrence. The report should contain as much information as possible and should be sent to:

Fax: + 44 1923 251137

Email: GlobalClinicalSAE@glenmarkpharma.com

When further information becomes available, the Pregnancy Report Form should be updated with all new information and reported immediately via the same contact information above. The Pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, and this information must be sent to the Sponsor as above. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Additional information will be requested by the Sponsor as necessary.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study drug, must be promptly reported to the Sponsor.

13. TIMING OF STUDY ASSESSMENTS

Study procedures and assessments are summarized within the Schedule of Assessments (Table 2).

13.1. Screening: (Day -3 to Day 0)

- **Screening (Day -3 to Day 0):**

- Screening should occur within 4 days before the Randomization. Before performing any procedures or assessments, the nature of the study and the potential risks associated with the study must be explained to all subjects and written informed consent must be obtained. Once informed consent has been obtained, the following procedures and evaluations will be performed:
    - Informed Consent
    - Demographics
    - Review Inclusion/Exclusion Criteria
    - Medical History
    - SARS CoV2 RT-PCR
    - Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)
    - Physical Examination
    - Vital Signs, Body Weight
    - Height

- SpO_2
- Pregnancy Test (serum)
- CXR/CT scan lung
- Lab Assessments (Hematology, Blood chemistry, Uric acid)
- Creatinine and Urine – routine, microscopy
- Efficacy assessment
- Safety Assessment
- Prior and Concomitant medications

- Subjects, who fail Screening on any single criterion, will not be rescreened

- The eligibility of a subject with respect to laboratory criteria will be assessed according to the local laboratory result for the Screening sample(s).

13.2. Randomization/Baseline (Day 1)

- Review Inclusion/Exclusion Criteria
- Randomization
- SARS CoV2 RT-PCR
- Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)
- Physical Examination
- Vital Signs, Body Weight
- SpO_2
- Pregnancy Test (serum)
- ECG
- Efficacy assessment
- Safety Assessment
- Prior and Concomitant medications
- Dispense Study medication

13.3. Day 2 to Day 14

- SARS CoV2 RT-PCR
- Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)
- Physical Examination
- Vital Signs, Body Weight
- Oxygen support/NIV/MV/ECMO support
- SpO_2
- Efficacy assessment
- Safety Assessment
- Administration of study medication

Lab tests can be repeated as per standard management for COVID-19

13.4. Day 15 to Day 28

- SARS CoV2 RT-PCR
- Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)
- Physical Examination
- Vital Signs, Body Weight
- Oxygen support/NIV/MV/ECMO support
- SpO2
- Efficacy assessment
- Safety Assessment
- Prior and Concomitant medications

Lab tests can be repeated as per standard management for COVID-19

13.5. Day of Discharge

- SARS CoV2 RT-PCR
- Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)
- Physical Examination
- Vital Signs, Body Weight
- SpO_2
- Lab Assessments (Hematology, Blood chemistry, Uric acid)
- Creatinine and Urine – routine, microscopy
- Efficacy assessment
- Safety Assessment
- Prior and Concomitant medications

Treatment duration is a maximum of 14 days and the total study duration will be maximum for 28 days from randomization. All the subjects will be hospitalized as per current standard of treatment and will be discharged only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative. The Day of Discharge from the treatment will occur based RT- PCR negative.

14. STATISTICS

The statistical analysis will be coordinated by the responsible Glenmark biostatistician. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized before the database lock at the latest. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

All analyses will be performed using SAS® Version 9.4 or above.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

14.1. Sample Size

Based on the hazard ratio (HR) of 3.434 in the paper by Q. Cai et al, total 28 viral clearance events (i.e. viral clearance patients) in each population need to be observed in order to obtain 90% power, a sample size of 40 to 100 is required in each mild and moderate population. In accordance with regulatory recommendations 90 subjects will be enrolled in mild Covid-19 sub-group and 60 subjects will be enrolled in moderate Covid-19 subgroup and a total sample size of 150 will be enrolled in the study.

14.2. Analysis Sets

14.2.1.1. All Patients Set

All randomized patients will be included in the All Patients Population. All data listings will be based on this population. Where listings are separated by treatment arm, safety data listings will be grouped by actual study treatment received and all other listings will be grouped by treatment randomized. Given that only randomized patients are entered onto the study database, it is implicit that the All Patients Population will comprise all patients in the study database.

14.2.1.2. Intent-to-Treat (ITT) Set

All randomized patients will be included in the intent-to-treat (ITT) population. All efficacy analyses will be based on the treatment arm to which the patients were randomized. Given that only randomized patients are entered onto the study database, it is implicit that the ITT Population will comprise all patients in the study database. The ITT population is the same as the All Patients population used for data listings, where data are reported by randomized treatment.

14.2.1.3. Per protocol analysis set (PPS)

A per protocol analysis population is not being defined for this study. The protocol violations will be documented according to the inclusion and exclusion criteria to be used as information in the Clinical Study Report (CSR). The only major protocol violation defined for this study is no study medication taken, which will lead to exclusion from the Safety Analysis Population. Violations of protocol-defined inclusion/exclusion criteria and on-study protocol violations will be classified as minor violations, and will not lead to exclusion from any analysis population.

14.2.1.4. Safety Analysis Set (SAS)

All patients randomized who have received any amount of study medication will be included in the Safety Analysis Set (SAS). By assumption patients who have received any amount of study medication are assumed to have had the opportunity to report adverse event safety data regardless of whether they have any post-baseline safety assessments recorded and will be included in the SAS. All safety analyses will be based on the treatment the patients actually received such that a patient who received any dose of Favipiravir will be included in the Favipiravir arm (regardless of whether this was intended).

Other Analysis Populations

No additional analysis populations are defined. However, it should be noted that for certain outcomes, the analysis may be based on sub-sets of the ITT population, as the outcome may only be relevant for specific patients. For objective response rate and time to response, only patients with measurable disease at baseline will be included in the analysis.

Outputs by Treatment Received

If any patients are randomized but not treated, listings produced for all patients by treatment received will include patients under the category 'Treatment Not Given'.

Patients who receive one or more administrations of Favipiravir at any time during the study will be reported under 'Favipiravir' arm as opposed to 'Standard Supportive Care' arm even if this administration was given in error (i.e. the patient was randomized to receive placebo but received one or more doses of Favipiravir).

14.3. Endpoints

14.3.1. Primary Endpoint

- Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days] (Time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab).

14.3.2. Secondary Endpoint(s)

- Time from randomization to clinical cure based on clinician assessment (Recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours; defined as(axillary temperature ≤ 97.8°F; respiratory rate ≤ 20 times/min; Oxygen saturation ≥ 98% without oxygen supplementation; mild or no cough).*
- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge
- Frequency of serious adverse events

  Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier.

*For those patients who presented with clinical signs and symptoms at baseline.

14.4. Subject Disposition

The number and proportion of subjects who complete the study or discontinue the study prematurely along with the reason for discontinuation will be presented.

The number and proportion of subjects who are screened but did not continue into the treatment period will be presented, along with the reason for discontinuation.

The number and proportion of subjects in each analysis set will be presented by treatment group.

14.5. Demographic and Other Baseline Characteristics

Subject demography information will be collected at Screening. Demography information includes date of birth (or age), sex, race/ethnicity etc.

14.6. Efficacy Analyses

Analysis of Primary Efficacy Endpoint

The primary endpoint will be analyzed using the Kaplan-Meier method and log-rank test. Potential influencing factors of viral clearance will be analyzed by Cox regression model. In the Cox model, the time of viral clearance was set as the Time variable, viral clearance (0 = no, 1 = yes) was set as the status, and the variables including age and independent variables.

Sub-group analysis will be done for the mild and moderate population for the primary endpoint.

Analysis of Secondary Efficacy Endpoint(s)

The following time event endpoints will be analyzed the same way as the primary endpoint using the Kaplan-Meier method, log-rank test and Cox analysis.

- Time from randomization to clinical cure based on clinician assessment (Recovery of fever, respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours) defined as (axillary temperature $\leq$ 97.8°C; respiratory frequency $\leq$ 20 times/min; Oxygen saturation $\geq$ 98% without oxygen inhalation; mild or no cough).*
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge

  Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier.

The following time event endpoints will be analyzed using the chi-square test or Fisher's exact test.

- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14

Sub-group analysis will be done for the mild and moderate population for secondary efficacy endpoints.

14.7. Pharmacokinetic, Pharmacodynamic, Biomarker, and Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

14.8. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

14.8.1. Extent of Exposure

The duration of exposure to study treatment will be summarized by treatment group.

14.8.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class, and having each individual AE (preferred term). Summaries will also be presented for AEs by event severity and for study treatment-related AEs. Subjects will be counted only once for each preferred term, system organ class, and by the highest severity of an event.

Separate summaries will be provided for death, SAE, AEs leading to discontinuation.

14.8.3. Laboratory Values

Laboratory evaluations will be summarized with descriptive statistics at the days, and change from baseline summarized for each post-randomization. Laboratory measurements may also be summarized based on the number and percentage of subjects above or below a pre-specified threshold. All laboratory data will be displayed in listings.

14.8.4. Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. All vital signs data will be displayed in listings.

14.8.5. Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group [or treatment or dose, depending on the study design].

14.8.6. Other Safety Analyses

Not applicable

14.9. Other Analyses

Not applicable

14.10. Interim Analysis

Early readouts of efficacy and safety may be performed after minimum 14 patients achieved viral clearance (RT PCR negative).

14.11. Data Safety Monitoring Committee

No formal DSMB is planned. Data will be reviewed by a scientific committee comprising of members from Clinical Development and Medical Affairs and Statistician.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit/evaluate the investigational study site remotely to:

- Determine the adequacy of the facilities
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available if the Investigator or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

15.2.1. Inspection

An inspection is defined as the act of a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsor's and/or CRO facilities or any other establishments deemed appropriate by the regulatory authorities.

15.2.2. Audit

An audit is a systematic and independent review of study-related activities and documents to determine whether study-related activities were conducted and the data were accurately recorded and analyzed according to the protocol, SOPs, GCP, and the appropriate requirements.

In conducting this study the Investigator accepts that the Sponsor, IRB/IEC or regulatory body may, at any time by appointment, conduct an audit of the study site.

15.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the clinical study. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, The Sponsor may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study, as well as any materials (eg diaries, questionnaires) to be given to subjects. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP guidelines, applicable regulatory requirements and the Sponsor's policy on Bioethics.

17.3. Written Informed Consent

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator is responsible for obtaining informed consent from each subject/legally acceptable representative (LAR) participating in the study. All pertinent aspects of the study must be explained to the subject/LAR before he or she signs the informed consent. The subject's signed and dated informed consent must be obtained before conducting any study procedures.

Informed consent must be obtained from the subject/LAR before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic screening procedures and the administration of the first dose of the study medication. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject/LAR should understand the statement before signing and dating it and will be given a copy of the signed document.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

17.4. Financial Disclosure

Investigators and Sub-investigators will provide Glenmark (or its designee) with sufficient, accurate financial information as requested to allow Glenmark, or its designee, to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

18. DATA HANDLING AND RECORDKEEPING

18.1. Data Collection

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards, laboratory reports, ECG strips, etc.

Subject demographics <and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors> will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not assigned to treatment/randomized into the study, the reason the subject was not assigned to treatment/randomized, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), will also be collected.

18.2. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.3. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.4. Financing and Insurance

The Sponsor will provide clinical study insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

19. PUBLICATION POLICY

The Sponsor recognizes and supports the publication and dissemination of scientific information as a means of furthering knowledge. The general strategy regarding publication of the study (what, when, where, etc.) will be mutually agreed upon by the Investigator and Sponsor. However, in order to protect its commercial interests, the Sponsor reserves the right to manage the publication of all study results. The Investigator agrees that oral and written communication to third parties of any procedures or results from the study is subject to prior written consent of the Sponsor. Presentation material and/or manuscript(s) for publication will be reviewed by Sponsor prior to submission for publication. This review will be completed within 30 days of receiving presentation material and 60 days of receiving the manuscript from the Investigator. Alterations in the material will only be made in agreement between the Investigator and the Sponsor.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

20. LIST OF REFERENCES

Avigan Tablet 200 mg- Deliberation Results by PMDA. (2014). Favipiravir: Report on the Deliberation Results; Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau; Ministry of Health, Labour and Welfare; March 4, 2014.

Q. Cai, M. Yang, D. Liu et al., Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, Engineering, https://doi.org/10.1016/j.eng.2020.03.007

Chen C, Huang J, Cheng Z et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv preprint doi: https://doi.org/10.1101/2020.03.17.20037432.

Hayden F and Shindo N. Influenza virus polymerase inhibitors in clinical development. Curr Opin Infect Dis. 2019 Apr; 32(2): 176–186.

Prescribing Information for Avigan Tablets 200 mg, Favipiravir. Manufactured and Marketed by: Toyama Chemical Co., Ltd. 2-5, Nishishinjuku 3-chome, Shinjuku-ku, Tokyo 160-0023, Japan, Revised, November 2017 (4th Version).

Sanders JM, Monogue ML, Jodlowski TZ et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020 Apr 13.

Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-Ncov) in vitro. Cell Res. 2020 Mar;30(3):269-271.

21. APPENDICES

APPENDIX 1. LIST OF CONTACT DETAILS

Additional information and contact details related to the study will be provided to each clinical site separately in relevant documents and procedural manuals.

SAE and Pregnancy Reporting:
Fax: + 44 1923 251137
Email: GlobalClinicalSAE@glenmarkpharma.com

Dr. Pawan Singh
Deputy General Manager | Clinical Development
Glenmark Pharmaceuticals
Andheri East, Mumbai- 400099
E-mail: Pawan.singh@glenmarkpharma.com

Dr. Rahul Kodgule
General Manager | Clinical Development
Glenmark Pharmaceuticals
Andheri East, Mumbai- 400099
E-mail: Rahul.Kodgule@glenmarkpharma.com

Dr Monika Tandon
Glenmark Pharmaceutical Ltd.
Andheri (E), Mumbai-99
Phone: +91 22 4018 9847
Mobile: +91 9930557454
E-mail: Monika.Tandon@glenmarkpharma.com

Amol Pendse
Glenmark Research Centre, A-607,
MIDC Mahape, Navi Mumbai 400709
Phone: +91 22 6772 0000 (Extn) 3502
Mobile: +91 9167256463
E-mail: Amol.Pendse@glenmarkpharma.com

APPENDIX 2. CLINICAL LABORATORY TESTS

Table 3: Clinical Laboratory Tests

Panel	Test to be performed
Hematology	Hemoglobin hematocrit red blood cell (RBC) count mean corpuscular volume (MCV) mean corpuscular hemoglobin concentration (MCHC) white blood cell (WBC) count with differential (absolute number and percentages) platelet count
Serum Chemistry	alanine transaminase (ALT) albumin alkaline phosphatase (ALP) aspartate transaminase (AST) bicarbonate blood urea nitrogen (BUN) calcium chloride cholesterol (total, LDL, HDL) creatinine creatinine clearance creatine phosphokinase gamma blutamyl transferase (GGT) glucose (specify if fasting or non-fasting) lactic dehydrogenase (LDH) magnesium phosphorus potassium sodium total bilirubin (direct and indirect) total protein triglycerides uric acid C-reactive protein
Urinalysis	Color appearance pH specific gravity presence of blood, glucose, protein, ketones, bilirubin, urobilinogen, nitrite microscopy including WBC/high power field (HPF), RBC/HPF

Table 3: Clinical Laboratory Tests (Continued)

Panel	Test to be performed
Pregnancy Testing	serum beta-human chorionic gonadotropin (serum β-hCG)
Virus Serology	Hepatitis A antibody Hepatitis B core antibody (HBcAb) Hepatitis B surface antigen (HBsAg) Hepatitis C antibody HIV-1 antibody HIV-2 antibody
Other	SARS CoV2 RT-PCR SpO_2

APPENDIX 3. PRESCRIBING INFORMATION FOR AVIGAN TABLETS

Prescribing Information for Avigan Tablets 200 mg, Favipiravir. Manufactured and Marketed by: Toyama Chemical Co., Ltd. 2-5, Nishishinjuku 3-chome, Shinjuku-ku, Tokyo 160-0023, Japan, Revised, November 2017 (4th Version).

STATISTICAL ANALYSIS PLAN
PHASE III

VERSION: 1.0
DATE OF PLAN: 10-JUL-2020

BASED ON:
ORIGINAL PROTOCOL, VERSION 3.0, 26-APR-2020

CRF, VERSION 1.0, 01-MAY-2020

STUDY DRUG: FAVIPIRAVIR

PROTOCOL NUMBER: GPL/CT/2020/002/III

STUDY TITLE: A RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF FAVIPIRAVIR COMBINED WITH STANDARD SUPPORTIVE CARE IN ADULT INDIAN PATIENTS WITH MILD TO MODERATE COVID-19

SPONSOR:

Glenmark Pharmaceuticals Ltd

Glenmark House,

B.D.Sawant marg,

Chakala,Andheri East,

Mumbai-400 099

India

Document Version History

Version Number	Version Date	Description of change
1.0	10-JUL-2020	1st version based on protocol version 3.0

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

The signatures on this page indicate review and approval of Statistical Analysis Plan.

I have reviewed the above-mentioned version of Statistical Analysis Plan and confirm it to be complete and accurate.		
Prepared by:		
Statistician	**Name: Dr Wen Wu** (Block Capital letters)	
	Signature:	**Date** (DD/MMM/YYYY):
Review and Approval :		
Medical Reviewer Protocol Author	**Name: Dr Pawan Singh** (Block Capital letters)	
	Signature:	**Date** (DD/MMM/YYYY):

STATISTICAL ANALYSIS PLAN
Protocol #GPL/CT/2020/002/III 10-JUL-2020

SIGNATURE PAGE

The signatures on this page indicate review and approval of Statistical Analysis Plan.

I have reviewed the above-mentioned version of Statistical Analysis Plan and confirm it to be complete and accurate.		
Prepared by:		
Statistician	**Name: Dr Wen Wu** (Block Capital letters)	
	Signature: Wen Wu	**Date** (DD/MMM/YYYY): Digitally signed by Wen Wu Date: 2020.07.10 18:53:20 +07'00'
Review and Approval :		
Medical Reviewer Protocol Author	**Name: Dr Pawan Singh** (Block Capital letters)	
	Signature: Pawan	**Date** (DD/MMM/YYYY): 10/Jul/2020

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company **Glenmark Pharmaceuticals Ltd**	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: Favipiravir 200 mg	**Page:**	
Name of Active Ingredient: Favipiravir 200 mg		
Title Of Study: A Randomized, Open-Label, Multicenter Study To Evaluate The Efficacy And Safety Of Favipiravir Combined With Standard Supportive Care In Adult Indian Patients With Mild To Moderate COVID-19.		
Studied period: Maximum of 28 days from randomization	**Phase of development:** Phase III	

Objectives:

Primary:

- The primary objective of this study is to evaluate the clinical efficacy of Favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

Secondary:

- The secondary objective is to evaluate the safety and tolerability of Favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

Methodology:

This is a randomized, multi-center, open-label, parallel arm, clinical study in Indian patients evaluating the efficacy and safety of Favipiravir with standard supportive care vs standard supportive care alone in mild to moderate COVID-19.

It is a parallel arm study with stratified randomization in which 150 eligible patients will be randomized in a 1:1 ratio into 2 groups: one group will receive Favipiravir along with standard supportive care and the control group will receive standard supportive care in accordance with latest guidelines issued by Ministry of Health and family welfare; Government of India. Treatment duration is a maximum of 14 days and the total study duration will be maximum for 28 days from randomization. The randomization will be stratified based on baseline disease severity into mild and moderate COVID-19 cases so that 90 subjects of mild and 60 subjects of moderate COVID-19 will get randomized into each strata. All the subjects will be hospitalized as per current standard of treatment and will be discharged only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative and clinical cure is achieved.

Number of Subjects (planned and analyzed):

Based on the hazard ratio (HR) of 3.434 in the paper by Q. Cai et al, total 28 viral clearance events (i.e. viral clearance patients) in each population need to be observed in order to obtain 90% power, a sample size of 40 to 100 is required in each mild and moderate population. In accordance with regulatory recommendations 90 subjects will be enrolled in mild Covid-19 sub-group and 60 subjects will be enrolled in moderate Covid-19 subgroup and a total sample size of 150 will be enrolled in the study.

Diagnosis and main criteria for inclusion:

Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Voluntarily participating in the clinical study; fully understanding and being fully informed of the study and having signed the Informed Consent Form (ICF); willingness and capability to complete all the study procedures
2. Age 18-75 years (inclusive) at the time of signing ICF
3. Patients with laboratory confirmation of infection with SARS-CoV-2 by positive RT-PCR (within 48 hours prior to randomization)
4. For female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pretreatment serum or urine pregnancy test
5. Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment;
6. Not participating in any other interventional drug clinical studies before completion of the present study.

Additional Inclusion criteria for mild cases only:

7. Time interval between symptoms onset and randomization to no more than 7 days
8. Pyrexia (temperature < 103.2ºF by Oral or thermal gun); respiratory rate 12 to ≤20/min
9. No more than four of the following of mild severity, and no more than two of moderate severity (Mild is defined as symptoms not requiring any or minimal therapeutic intervention; moderate is defined as symptoms which produce small impairment of function and require some form of therapeutic intervention; severe is defined as symptoms resulting in marked impairment of function):
    - Cough
    - Sore throat
    - Headache
    - Nasal congestion
    - Body aches and pains
    - Fatigue

Additional Inclusion criteria for moderate cases:

10. Patients with the interval between symptoms onset and randomization is no more than 10 days
11. Chest imaging (CT as first option or X-ray if CT not possible)-documented pneumonia
12. Patients with pyrexia (thermal gun ≥99.5ºF); respiratory rate >20 to <30/min

Exclusion criteria:

1. Where, in the opinion of the investigator, participation in this study will not be in the best interest of the subject, or any other circumstances that prevent the subject from participating in the study safely
2. Severe infection, defined as need for invasive or non-invasive ventilator support, ECMO or shock requiring vasopressor support.
3. Inability to intake or tolerate oral medications.
4. Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN
5. Gout/history of gout or hyperuricemia (above the ULN)
6. Prolonged QT, defined as QTcF ≥450 milliseconds for men and as QTcF ≥470 for women
7. Known severely reduced LV function (Ejection fraction <30%)

8. Oxygen saturation (SPO2) ≤ 93% or arterial oxygen partial pressure (PaO2)/ fraction of inspired O2 (FiO2)≤300 mmHg;
9. Requires ICU care for management of ongoing clinical status.
10. Known allergy or hypersensitivity to Favipiravir;
11. Known severe renal impairment [creatinine clearance (CrCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis;
12. Asthma or chronic obstructive lung disease
13. Psychiatric disease that is not well controlled (controlled defined as stable on a regimen for more than one year).
14. Pregnant or lactating women;
15. Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug.
16. Clinical prognostic non-survival, palliative care, and have no response to supportive treatment within three hours of admission.

Test product, dose and mode of administration:

Investigational Product

- ***Name of Investigational Product***: Favipiravir
- ***Dosage Form:*** tablet
- ***Dosage:*** Favipiravir 200mg
- ***Dosage Frequency:*** Favipiravir administered 1800 mg on the first dose (day 1) followed by 800 mg twice daily for maximum of the next 13 days (days 2 to maximum day -14). For 1800 mg dose in morning of Day 1, 9 tablets will be dispensed. Similar procedure will be repeated for Day 1 evening dose. From Day 2 onwards, 4 tablets will be dispensed in morning and 4 tablets in evening.
- ***Mode of Administration:*** Oral

Duration of treatment:

Maximum 14 days

Reference therapy, dose and mode of administration:

- ***Name of Control:*** Standard Supportive Care
- ***Dosage Form:*** NA
- ***Dosage:*** NA
- ***Dosage Frequency:*** NA
- ***Mode of Administration:*** NA

Criteria for evaluation:

Primary Endpoint:

- Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days]
  (Time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab).

Secondary Endpoints:

- Time from randomization to clinical cure based on clinician assessment*
- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge

  Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier.

  *For those patients who presented with clinical signs and symptoms at baseline.

Safety:

Frequency of serious adverse events.

*- Recovery of fever, Respiratory rate, oxygen saturation and cough relief that is maintained for at least 72 hours. The cut –off values provided in the protocol are indicative.

Statistical methods:

All Patients Set

All randomized patients will be included in the All Patients Population. All data listings will be based on this population. Where listings are separated by treatment arm, safety data listings will be grouped by actual study treatment received and all other listings will be grouped by treatment randomized. Given that only randomized patients are entered onto the study database, it is implicit that the All Patients Population will comprise all patients in the study database.

Intent-to-Treat (ITT) Set

All randomized patients will be included in the intent-to-treat (ITT) population. All efficacy analyses will be based on the treatment arm to which the patients were randomized. Given that only randomized patients, who receive at least one treatment and have at least one efficacy assessment post baseline, are entered onto the study database, it is implicit that the ITT Population will comprise all patients in the study database. The ITT population is the same as the All Patients population used for data listings, where data are reported by randomized treatment.

Per protocol analysis set (PPS)

A per protocol analysis population is not being defined for this study. The protocol violations will be documented according to the inclusion and exclusion criteria to be used as information in the Clinical Study Report (CSR). The only major protocol violation defined for this study is no study treatment (Favipiravir or Supportive Care alone) taken, which will lead to exclusion from the Safety Analysis Population. Violations of protocol-defined inclusion/exclusion criteria and on-study protocol violations will be classified as minor violations, and will not lead to exclusion from any analysis population.

Safety Analysis Set

All patients randomized who have received any amount of study treatment (Favipiravir or Supportive Care alone) will be included in the Safety Analysis Set. By assumption patients who have received any amount of study treatment are assumed to have had the opportunity to report adverse event safety data regardless of whether they have any post-baseline safety assessments recorded and will be included in the SAFETY ANALYSIS SET. All safety analyses will be based on the treatment the patients actually received such that a patient who received any dose of Favipiravir will be included in the Favipiravir arm (regardless of whether this was intended).

Other Analysis Populations

No additional analysis populations are defined. However, it should be noted that for certain outcomes, the analysis may be based on sub-sets of the ITT population, as the outcome may only be relevant for specific patients. For objective response rate and time to response, only patients with measurable value at baseline will be included in the analysis.

Outputs by Treatment Received

If any patients are randomized but not treated, listings produced for all patients by treatment received will include patients under the category 'Treatment Not Given'.

Patients who receive one or more administrations of Favipiravir at any time during the study will be reported under 'Favipiravir' arm as opposed to 'Standard Supportive Care' arm even if this administration was given in error (i.e. the patient was randomized to control arm, but received one or more doses of Favipiravir).

Patients who receive Standard Supportive Care and do not receive any administration of Favipiravir at any time during the study will be reported under control arm as opposed to 'Favipiravir' arm even if this was given in error (i.e. the patient was randomized to Favipiravir arm, but received no Favipiravir).

Analysis of Primary Efficacy Endpoint

The primary endpoint will be analyzed using the Kaplan-Meier method and log-rank test. Potential influencing factors of viral clearance will be analyzed by Cox regression model. In the Cox model, the time to event (i.e. negative SARS-CoV2 RT-PCR result) will be set as the Time variable, censoring (0 = no, 1 = yes) will be set as the status, and the variables including age, treatment and baseline co-morbidity (Hypertension, Diabetes, Obesity, cardiovascular disease and cerebrovascular disease) as independent variables.
Sub-group analysis will be done for the mild, moderate, different age-group populations for the primary endpoint.

Analysis of Secondary Efficacy Endpoints

The following time event endpoints will be analyzed the same way as the primary endpoint using the Kaplan-Meier method, log-rank test and Cox analysis.

- Time from randomization to clinical cure based on clinician assessment.
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge

The following time event endpoints will be analyzed using the chi-square test or Fisher's exact test.

- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14

Sub-group analysis will be done for the mild, moderate, different age-group populations for secondary efficacy endpoints.

Pharmacokinetic Analyses

No PK parameters will be calculated.

Interim Analyses

Early readouts of efficacy and safety may be performed after minimum 14 events of viral clearance (RT PCR negative) in about 30 subjects.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

AE	Adverse event
BP	Blood pressure
BUN	Blood Urea Nitrogen
C	Control
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CrCl	creatinine clearance
CSR	Clinical study report
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
HR	Hazard ratio
ICH	International Conference on Harmonisation
IP	Investigational product
ITT	Intention-to-treat
K-M	Kaplan-Meier
LDH	lactic acid dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MV	mechanical ventilation
NIV	Non-invasive ventilation
PaO2	arterial oxygen partial pressure
PPS	Per protocol set
PT	Preferred term
QT	Electrocardiographic QT interval from onset of Q wave to end of T wave
QTc	QT interval corrected for HR
R	a free software environment for statistical computing and graphics
REML	Restricted Maximum-Likelihood
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAS	SAS (previously "Statistical Analysis System") is a statistical software suite developed by SAS Institute for data management, advanced analytics, multivariate analysis, business intelligence, criminal investigation, and predictive analytics

SAP	Statistical analysis plan
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SOC	System organ class
SD	Standard deviation
SpO2	peripheral capillary oxygen saturation
T	Test drug
TEAE	Treatment emergent adverse event
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol GPL/CT/2020/002/III

Protocol Revision Chronology:		
Protocol	19-Apr-2020	Original
Amendment 1	23-Apr-2020	Version 2.0
Amendment 2	26-Apr-2020	Version 3.0

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Freeze of the study data. Further information can be found in the protocol.

3. STUDY OBJECTIVES AND ENDPOINTS

This document describes the Statistical Analysis Plan (SAP) for Glenmark Pharmaceuticals Limited, Protocol GPL/CT/2020/002/III with study entitled "A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Favipiravir Combined with Standard Supportive Care in Adult Indian Patients with Mild to Moderate COVID-19.".

This SAP will be developed and finalized prior to database lock.

Any changes to the SAP will require the new version of SAP to be released. The responsible parties at Glenmark Pharmaceuticals Limited will be required to review and approve all versions of the SAP before database lock.

3.1. Study Objectives

3.1.1. Primary Objective

- The primary objective of this study is to evaluate the clinical efficacy of Favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

3.1.2. Secondary Objective

- The secondary objective is to evaluate the safety and tolerability of Favipiravir combined with standard supportive care compared with standard supportive care alone in treating adult patients with mild to moderate COVID-19.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days] (Time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab)

3.2.2. Secondary Endpoints

- Time from randomization to clinical cure based on clinician assessment.*
- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14
- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge

- Note: All the end points will be evaluated from randomization until the date of hospital discharge or day 28; whichever is earlier.

  *For those patients who presented with clinical signs and symptoms at baseline.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a randomized, multi-center, open-label, parallel arm, clinical study in Indian patients evaluating the efficacy and safety of Favipiravir with standard supportive care vs standard supportive care alone in mild to moderate COVID-19.

It is a parallel arm study with stratified randomization in which 150 eligible patients will be randomized in a 1:1 ratio into 2 groups: one group will receive Favipiravir along with standard supportive care and the control group will receive standard supportive care in accordance with latest guidelines issued by Ministry of Health and family welfare; Government of India. Treatment duration is a maximum of 14 days and the total study duration will be maximum for 28 days from randomization. The randomization will be stratified based on baseline disease severity into mild and moderate COVID-19 cases so that 90 subjects of mild and 60 subjects of moderate COVID-19 will get randomized into each strata. All the subjects will be hospitalized as per current standard of treatment and will be discharged only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative and clinical cure is achieved.

4.2. Definition of Study Drugs

Investigational Product:

- Name of Investigational Product: Favipiravir
- Dosage Form: tablet
- Dosage: Favipiravir 200mg
- Dosage Frequency: Favipiravir administered 1800 mg on the first dose (day 1) followed by 800 mg twice daily for maximum of 13 days (days 2 to maximum day 14). For 1800 mg dose in morning of Day 1, 9 tablets will be dispensed. Similar procedure will be repeated for Day 1 evening dose. From Day 2 onwards, 4 tablets will be dispensed in morning and 4 tablets in evening.
- Mode of Administration: Oral

Comparator:

- Standard Supportive Care only

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

Based on the hazard ratio (HR) of 3.434 in the paper by Q. Cai et al, total 28 viral clearance events (i.e. viral clearance patients) in each population need to be observed in order to obtain 90% power with two-sided alpha of 0.05. Depending on the censoring rate and median time to event of the control arm, a sample size of 40 to 100 is required in each mild and moderate population. In accordance with regulatory recommendations 90 subjects will be enrolled in mild Covid-19 sub-group and 60 subjects will be enrolled in moderate Covid-19 subgroup and a total sample size of 150 will be enrolled in the study.

4.3.2. Sample Size Re-estimation

Sample size may be adjusted during the study if the real HR is very different from the assumed 3.434.

4.4. Randomization

A biostatistician at Glenmark prepared the randomization list for the study using R version 3.6.1 (2019-07-05).

4.5. Clinical Assessments

All clinical assessments are listed in the following table. The safety assessments to be performed in this study, including haematology analyses, blood chemistry tests, urinalysis, Imaging assessments, and assessment of adverse events (AE), are standard evaluations to ensure subject safety.

Schedule of Procedures and Assessments

Study Period	**Screening**	**Baseline**	**Evaluation Period**		
Time Point	**Day -3 to Day 0**	**Day 1**	**Day 2 to Day 14**	**Day 15 to Day 28**	**Day of Discharge[##]**
Informed Consent	√				
Demographics	√				
Review Inclusion/Exclusion Criteria	√	√			

Study Period	Screening	Baseline	Evaluation Period		
Time Point	**Day -3 to Day 0**	**Day 1**	**Day 2 to Day 14**	**Day 15 to Day 28**	**Day of Discharge[##]**
Randomization		√			
Medical history	√				
SARS CoV2 RT- PCR	√		√	√	√
Assessment of clinical symptoms (Cough, sore throat, headache, nasal congestion, body aches and pains, fatigue)*	√	√	√	√	√
Vital parameters (Body temp**, RR, BP, Pulse), Body weight*	√	√	√	√	√
Complete Physical Examination	√	√	√	√	√
Height	√				
Prior and concomitant medication	√	√	√	√	√
SpO_2	√	√	√	√	√
CXR/CT scan lung[1]	√				
Check for Oxygen support/NIV/MV/ECMO support		√	√	√	
ECG	√				
Laboratory parameters	√		#	#	√
Serum Pregnancy test[2]	√				

Study Period	Screening	Baseline	Evaluation Period		
Time Point	**Day -3 to Day 0**	**Day 1**	**Day 2 to Day 14**	**Day 15 to Day 28**	**Day of Discharge[##]**
Efficacy assessment*		√	√	√	√
Safety assessment	√	√	√	√	√
Administration of Study medication		√	√		

*Clinical examination, vitals and other patient care procedures will be done as per treating Physician. Clinical symptoms and Vital parameters will be assessed twice daily, morning and evening on day 1 to day 28.
**Axillary temperature will be taken, if not measured temperature at other sites will be taken.
Patient care requirement beyond Day 14 will be as per investigator judgment.
[1]Documented pneumonia based on Chest X-ray/CT scan lung within 24 hours from ICF 3 days.
[2]Female subjects of child bearing potential only, Serum β-HCG at screening.
Lab tests can be repeated as per standard management for COVID-19
[##]Day of Discharge from the treatment will occur based RT- PCR negative, clinical cure. The subject will be discharged from study only after 2 consecutive test for COVID-19 based on RT-PCR becomes negative.
Note: Recovery status check – If patient is getting recovered in less time and discharged that does not mean discontinued.
Additional procedures can be performed as per standard management for COVID-19.

All the assessments for Premature discontinuation will be considered on the Day of discharge. Both the recovered subjects and Premature discontinued subjects will be performed assessments on Day of Discharge

5. PLANNED ANALYSES

5.1. Interim Analyses

Early readouts of efficacy and safety may be performed after minimum 14 events of viral clearance (RT PCR negative) when about 30 subjects have completed the study.

5.2. Final Analyses

After completion of the clinical trial, a final analysis of data from 150 subjects will be planned.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings (e.g., post text tables and individual subject data listings are prepared according to ICH Guideline E3) include a "footer" providing explanatory notes that indicate as a minimum:

1. Date of data extraction.
2. Date of output generation.
3. SAS program name, including the path that generates the output.
4. The name of programmer and Date of outputs.
5. Any other output specific details that require further elaboration.

Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure the replication of the results.

In general, post text tables will be organized with respect to treatment group and a column will be included to summarize all treated subjects. For comparative studies, the order of drug presentation will be investigational drug first followed by placebo (if it exists) and all other active comparative agents. A total column can appear as the last column. When appropriate, tables will display sub-group differences by treatment group. Row entries in post text tables are made only if data exists for at least one subject (e.g., a row with all zeros will not appear). The only exception to this rule applies to tables that summarize the study termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Summary tables for medications and medical conditions are coded according to standard dictionaries (e.g., WHO Drug standard dictionary, Sep 2018 version). Adverse event preferred terms and body/organ systems are coded using dictionaries, such as, WHO ART, COSTART, and MedDRA. The MedDRA dictionary can be used, as well, in the coding of signs and symptoms, medical history, physical examination abnormalities, and clinical diagnoses to map to MH, AE, and Concomitant Procedures module .

Supportive individual Subject Data Listings, as a minimum, are sorted and presented by treatment group (group) and investigational site (center). Listings also include subject number, visit number, visit date, and days relative to the initiation of double-blind treatment.

Other subject data listings that do not support a specific summary table are included to provide an enumeration of the investigator's general comments. This listing is also organized by treatment group and by investigator. Sorting is also performed with respect to subject, reference visit number and date, visit relative day, date of the comment, and the text of the comment.

No imputations are imposed for missing clinical data. Specific algorithms, however, can be discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data should be flagged in the individual subject data listings. Imputed data are not incorporated into any raw or primary datasets. These data are retained in derived analysis datasets.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The default convention is to number tables and listings using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number should be consistent with the corresponding CSR appendix in which the tables or listings will appear. For example, the post text tables usually occupy Appendix 14 and the individual subject data listings are put in Appendix 16. All post text tables should have a main number level 14 and listings 16. The subject accounting and disposition table is usually first in the first section of the report and should be numbered Table 14.1. The supportive subject data listing would be Listing 16.1.
2. Subject accounting and final disposition should appear as the second level number (Table 14.1 series). Baseline and demographic profile occupies the next sub-level (Table 14.1.2 series). Efficacy should come next (14.2 series) followed by safety (table 14.3 series). Reasons for subjects' being excluded from efficacy and protocol violation summary tables should appear as the last level (Table 14.4 series). Similar conventions should be applied to the subject data listings.
3. The title should be complete, accurate, and concise. The last line of the title should provide the analysis group being summarized (e.g., Intent-to-Treat Subjects or Per-Protocol Efficacy Subjects). If possible, the units of measurement for data contained in the table can appear in parentheses to conserve space in the body of the table. For example, the summary of vital signs title could read "Summary of Sitting and Supine Blood Pressure (mmHg) and Heart Rate (bpm)." Whether in the title or body of a table or listing, units must always be specified for all appropriate data.
4. If possible, variables being summarized and statistics reported should appear in the left most column of a table. The next columns for treatment groups should report the data from left to right for the investigational drug, placebo, comparative agents, and (optional) all treated subjects, respectively.

In general, the listings should be sorted and presented by treatment assignment, investigational site, and subject number. Treatment assignment and site can appear in the banner of the listing. From left to right, the subject number, visit number, visit date, and relative day should appear. All tables and listings must have explanatory notes that give, as a minimum, data extraction date, output generation date, programmer name, complete program name and path where it is stored, CRF pages from which the data were obtained, and supportive listings or tables supported, as appropriate. The definition of all derived variables and decodes for coded data must appear in the notes. Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.

Tables, Listings and Figures are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. Additional Tables, Figures and Listings will be generated, as needed, following the data analysis (post-hoc).

6.3. Data Management

Study data will be entered into CRFs. Before data analysis, programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data. All issues resulting from the computer-generated checks will be resolved.

6.4. Data Presentation Conventions

Continuous variables (e.g. age) are summarized using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), median and minimum and maximum). Categorical variables (e.g. race) are summarized using counts and percentages. Percentages are calculated using the total subjects per treatment group.

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be decimal aligned.

- P-values, if applicable, will be presented to 4 decimal places. If the p-value is less than 0.0001 then it will be presented as <0.0001. If the rounded result is a value of 1.000, it will be displayed as >0.9999.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

The table and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

6.5. Analysis Populations

All Patients Set

All randomized patients will be included in the All Patients Population. All data listings will be based on this population. Where listings are separated by treatment arm, safety data listings will be grouped by actual study treatment received and all other listings will be grouped by treatment randomized. Given that only randomized patients are entered onto the study database, it is implicit that the All Patients Population will comprise all patients in the study database.

Intent-to-Treat (ITT) Set

All randomized patients will be included in the intent-to-treat (ITT) population. All efficacy analyses will be based on the treatment arm to which the patients were randomized. Given that only randomized patients, who receive at least one treatment and have at least one efficacy assessment post baseline, are entered onto the study database, it is implicit that the ITT Population will comprise all patients in the study database. The ITT population is the same as the All Patients population used for data listings, where data are reported by randomized treatment.

Per protocol analysis set (PPS)

A per protocol analysis population is not being defined for this study.

Safety Analysis Set

All patients randomized who have received any amount of study treatment (Favipiravir or Supportive Care alone) will be included in the Safety Analysis Set. By assumption patients who have received any amount of study treatment are assumed to have had the opportunity to report adverse event safety data regardless of whether they have any post-baseline safety assessments

recorded and will be included in the SAFETY ANALYSIS SET. All safety analyses will be based on the treatment the patients actually received such that a patient who received any dose of Favipiravir will be included in the Favipiravir arm (regardless of whether this was intended).

Other Analysis Populations

No additional analysis populations are defined. However, it should be noted that for certain outcomes, the analysis may be based on sub-sets of the ITT population, as the outcome may only be relevant for specific patients. For objective response rate and time to response, only patients with measurable value at baseline will be included in the analysis.

Outputs by Treatment Received

If any patients are randomized but not treated, listings produced for all patients by treatment received will include patients under the category 'Treatment Not Given'.

Patients who receive one or more administrations of Favipiravir at any time during the study will be reported under 'Favipiravir' arm as opposed to 'Standard Supportive Care' arm even if this administration was given in error (i.e. the patient was randomized to control arm, but received one or more doses of Favipiravir).

Patients who receive Standard Supportive Care and do not receive any administration of Favipiravir at any time during the study will be reported under control arm as opposed to 'Favipiravir' arm even if this was given in error (i.e. the patient was randomized to Favipiravir arm, but received no Favipiravir).

6.6. Baseline Definition

The Baseline value will be defined as pre-dose measurement at day 1 or the last non-missing value prior to first dose date.

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Age at baseline will be calculated as follows:

- Baseline Age (years) = FLOOR((date of informed consent – date of birth day +1)/365.25).

6.7.2. Treatment Day

Study day will be computed by subtracting the date of the first dose of study drug from the date of last dose and adding one. Thus, the first day of dosing is defined as Day 1.

- Treatment days = last dose date – first dose date + 1.

6.7.3. Change from Baseline

Change from baseline will be calculated by subtracting the baseline measurement from the post baseline measurement.

- Change from baseline = post baseline measurement – baseline measurement.

Percent change from baseline is calculated as (change from baseline/baseline result * 100). If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.7.4. Handling laboratory data out of the range of quantification

If any laboratory value falls above or below the upper or lower level of quantification, the value of the upper or lower level of quantification will be taken (e.g. <0.2 will become 0.2) for summaries but left as recorded in the listing.

6.8. Handling of Missing Data

6.8.1. Missing Efficacy Endpoints

Censoring is used to deal with missing data in which time to event is not observed for reasons such as termination of study before all recruited subjects have shown the event of interest or the subject has left the study prior to experiencing an event. Subjects who terminated the study without documented event are censored at day 28. Subjects who die without documented event are censored at day 28 or the date of death whichever is later.

6.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

- If year and month are present and day is missing, then set day to first day of month for start date, and set day to last day of month for end date
- If year and day are present and month is missing, then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing, then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing date will not be imputed

The partial dates will be provided as imputed dates in the subject data listings.

6.8.3. Missing Start and Stop Dates for Adverse Events

Due diligence will be done to obtain accurate AE information. If all planned methods to obtain accurate AE information have failed, missing and partial AE onset and end dates will be imputed. Imputed dates will be flagged in the individual supportive subject listings. Unless otherwise specified, the following conventions will be used:

Missing and Partial AE onset dates:

- If onset date is completely missing, then onset date is set to date of first dose
- If onset year is present and month and/or day are missing:
  - If onset year = year of first dose, then set onset date to date of first dose
  - If onset year < year of first dose, then set onset month and day to December 31st.
  - If onset year > year of first dose, then set onset month and day to January 1st
- If onset month and year are present and day is missing:

  If onset year = year of first dose and
  - onset month = month of first dose then set onset date to date of first dose
  - onset month < month of first dose then set onset date to last day of month
  - onset month > month of first dose then set onset date to 1st day of month

  If onset year < year of first dose then set onset date to last day of month

  If onset year > year of first dose then set onset date to 1st day of month
- For all other cases, set onset date to date of first dose

Missing and Partial AE end dates:

- If end date is completely missing, end date is not imputed and the AE is flagged as "ongoing"
- If year is present and month and/or day are missing
  - If year = year of last dose, then set end date to the date of last dose
  - If year < year of last dose, then set end month and day to December 31st
  - If year > year of last dose, then set end month and day to January 1st
- If month and year are present and day is missing:

If year = year of last dose and

- month = month of last dose then set day to day of last dose
- month < month of last dose then set day to last day of month
- month > month of last dose then set day to 1st day of month

If year < year of last dose, then set end date to last day of the month

If year > year of last dose, then set end date to 1st day of month

- For all other cases, set end date to date of last dose

7. STUDY POPULATION

7.1. Subjects Disposition

A detailed description of the subject disposition will be provided by treatment arm. It will include the following:

- A definition of subjects enrolled (per arm) in the trial
- A summary of data on subject completion and discontinuation

7.2. Screen Failures

Subjects who give informed written consent but are not dispensed study medication are considered screen failures. In general, no attempt will be made to further characterize the reason for screen failures in summary tables due to the paucity of information usually gathered. Number and percentage of subjects who were screened for the study and screen failure will be summarized.

7.3. Protocol Deviations

The only major protocol violation defined for this study is no study treatment (Favipiravir or Supportive Care alone) taken, which will lead to exclusion from the Safety Analysis Population. Violations of protocol-defined inclusion/exclusion criteria and on-study protocol violations will be classified as minor violations, and will not lead to exclusion from any analysis population.

A by-subject listing of major protocol deviations will be provided. In addition, the number and percentage of subjects who completed study treatment and discontinued study treatment before end of study Day will be summarized, along with the reason.

7.4. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized on the safety populations.

Age (calculated from the date of birth), sex, disease severity, disease signs and symptoms at screen will be summarized with descriptive statistics for each treatment arm.

7.5. Listing of Subject Inclusion and Exclusion Criteria

Subjects meeting any of the inclusion and exclusion criteria will be listed along with the reason. Any subject withdrawal during the study, along with the reason for withdrawal, will be documented in listings.

7.6. Prior and Concomitant Medications

Prior and Concomitant medications on study subjects collected and the conditions mentioned in study protocol will be summarized and provide listings.

7.7. Baseline Laboratory Data

Baseline for laboratory results is defined as the last assessment just prior to the first dose of study medication (Day 1) regardless of whether it was scheduled, retest, or unscheduled. All treated subjects with a baseline laboratory determination will be included. Summary tables are present for each category of data separately. Routine clinical laboratory data usually include hematology, serum chemistry, and urinalysis. Quantitative laboratory test result summaries will include N, mean, s.d., median, and range. Qualitative tests will be categorized accordingly. The set of laboratory parameters included in each table will correspond to those requested in the study protocol.

Subject data listings will include the laboratory test, test units, laboratory test result, and the laboratory standard normal ranges, if available.

7.8. Baseline Primary and Secondary Efficacy Evaluations

Not applicable.

8. METHOD OF ANALYSIS

All the efficacy and safety parameters will be analyzed till 28 days.

AEs and SAEs beyond 28 days will be monitored and reported in the analysis for extension phase. AEs and SAEs which are still on going at 28 days will be monitored and reported in the study analysis at 28 days. Which means, all AEs occurred during 28 days and completed after 28 days, will be included in the analysis for 28 days, as start date of AE occurred on/before 28 days.

All efficacy endpoint will be analyzed using ITT Population.

The statistical analysis will be performed using the statistical software SAS 9.4 version or latest available (SAS Institute Inc., Cary, North Carolina).

Quantitative data will be summarized using number of subjects, mean, standard deviation, median, minimum and maximum.

Qualitative data will be summarized using frequency and percentage.

Time to event data will be summarized using no of patients, no of events and percentage, no of censored patients and percentage.

Categorical variables will be compared between the treatment arms using chi-square/Fisher's exact test as appropriate.

Time to event variables will be analyzed using the Kaplan-Meier method to generate the K-M plot and to calculate the median time to event and its 95% confidence interval (CI) for each arm. log-rank test will be used to calculate the p-value to compare the two arms. Cox regression model will be used to calculate the hazard ration (HR) of the test vs control and its 95% CI.

9. EFFICACY

9.1. Analysis of the Primary Efficacy Endpoint

9.1.1. Primary Efficacy Analysis

The primary endpoint will be analyzed using the Kaplan-Meier method and log-rank test. Potential influencing factors of viral clearance will be analyzed by Cox regression model. In the Cox model, the time to event (i.e. negative SARS-CoV2 RT-PCR result) will be set as the Time variable, censoring (0 = no, 1 = yes) will be set as the status, and the variables including age, treatment and baseline co-morbidity (Hypertension, Diabetes, Obesity, cardiovascular disease and cerebrovascular disease) as independent variables.

Patients who do not have documented negative SARS-CoV2 RT-PCR event at the time of the data cut-off for the primary efficacy analysis will be censored at the day 28. Patients who have died within 28 days who have no documented event, will be censored at day 28. Patients who have died after 28 days who have no documented event, will be censored at date of death.

The null hypothesis ($\mathbf{H_0}$) is that the survival distributions of the primary endpoint in the two treatment arms (denoted as $\mathbf{S_{<Test\text{-}drug>}}$ or $\mathbf{S_{<Control>}}$) are the same. The alternative hypothesis ($\mathbf{H_1}$) is that the survival distribution in the treatment arm and the control arm are different:

$$\mathbf{H_0:\ S_{<Test\text{-}drug>} = S_{<Control>}} \qquad \textbf{vs.} \qquad \mathbf{H_1: S_{<Test\text{-}drug>} \neq S_{<Control>}}$$

The log rank test will be used to compare the distributions between treatment arms. The Kaplan-Meier approach will be used to estimate the median time to event for each treatment arm and the corresponding two-sided 95% CI. The Cox proportional hazard model will be used to estimate the hazard ratio (HR) between the two treatment arms and its 95% confidence interval (CI).

If HR (T/C) is higher than 1 and the p-value is less than 0.05, one can claim the Test arm is superior to the Control arm.

9.1.2. Other Analyses of the Primary Efficacy Results

Sub-group analysis will be done for the mild, moderate and different age-group populations for the primary endpoint.

9.2. Analysis of the Secondary Endpoints

The following time event endpoints will be analyzed the same way as the primary endpoint using the Kaplan-Meier method, log-rank test and Cox analysis.

- Time from randomization to clinical cure based on clinician assessment.

- Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal membrane oxygenation
- Time from randomization to hospital discharge

The following time event endpoints will be analyzed using the chi-square test or Fisher's exact test. Rate will only account the number of events which were happened before day 4/7/10/14.

- Rate of Clinical cure at day 4/7/10/14
- Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14

Sub-group analysis will be done for the mild, moderate and different age-group populations for secondary efficacy endpoints.

9.3. Summary of Endpoint Analyses

Table below summarizes all of the endpoint analyses that will be done and the analysis methods and populations.

Endpoint	Analyses	Population (s)
1. Time until cessation of oral shedding of SARS-CoV-2 virus	Kaplan-Meier method, log-rank test and Cox regression	ITT
2. Time from randomization to clinical cure based on clinician assessment	Kaplan-Meier method, log-rank test and Cox regression	ITT
3. Time from randomization to first time use of high flow supplemental oxygen/non-invasive ventilation/mechanical ventilation/ extracorporeal	Kaplan-Meier method, log-rank test and Cox regression	ITT

membrane oxygenation		
4. Time from randomization to hospital discharge	Kaplan-Meier method, log-rank test and Cox regression	ITT
5. Compliance with the study medication	Summary Statistics	Safety analysis Set
6. Rate of Clinical cure at day 4/7/10/14	Chi-square test or Fisher's exact test	ITT
7. Rate of SARS-CoV2 RT-PCR negativity in both oropharyngeal swab and nasopharyngeal swab at day 4/7/10/14	Chi-square test or Fisher's exact test	ITT
8. Number and percentage of patients with treatment emergent adverse events (TEAE)	Summary Statistics	Safety analysis Set

10. SAFETY ANALYSES

10.1. Compliance

The compliance will not be reported as the patients are all hospitalized and site staff will give the tablets.

10.2. Adverse Events

The investigator's verbatim term of each AE will be mapped to system organ class and preferred term using the MedDRA Version 23.0 or latest available.

Adverse events will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment group.

The TEAEs will be defined as an event not present prior to exposure to the treatment or, if present prior to exposure, an event, which worsens in either intensity or frequency following exposure to the treatment.

Subject counts and percentages with event will be presented for each treatment groups and totaled for all treatment groups for the following summaries:

1. All AEs
2. All treatment emergent adverse events (TEAEs)
3. TEAEs by relationship to study drug
4. TEAEs by Severity
6. Serious treatment emergent adverse events (TEAEs)
7. TEAEs leading to death
8. TEAEs leading to permanent discontinuation of study drug.
9. Summary of Frequency Categories of TEAEs for Favipiravir.

Drug related AEs will be defined as AE with relationship to study drug as 'Yes'.

If subject has more than one episode of an AE, subject will be counted only once in system organ class (SOC) and once for specific preferred term (PT).

Listings will be presented by subject for all adverse events.

10.3. Routine Laboratory Data

Clinical laboratory results at each time point and for change from baseline will be displayed using summary statistics.

The safety laboratory tests are as follows:

Panel	Test to be performed
Hematology	Hemoglobin hematocrit red blood cell (RBC) count mean corpuscular volume (MCV) mean corpuscular hemoglobin concentration (MCHC) white blood cell (WBC) count with differential (absolute number and percentages) platelet count
Serum Chemistry	alanine transaminase (ALT) albumin alkaline phosphatase (ALP) aspartate transaminase (AST) bicarbonate blood urea nitrogen (BUN) calcium chloride cholesterol (total, LDL, HDL) creatinine creatinine clearance creatine phosphokinase gamma blutamyl transferase (GGT) glucose (specify if fasting or non-fasting) lactic dehydrogenase (LDH) magnesium phosphorus potassium sodium total bilirubin (direct and indirect) total protein triglycerides uric acid C-reactive protein
Urinalysis	Color appearance pH specific gravity presence of blood, glucose, protein, ketones, bilirubin, urobilinogen, nitrite microscopy including WBC/high power field (HPF), RBC/HPF

Pregnancy Testing	serum beta-human chorionic gonadotropin (serum β-hCG)
Other	SARS CoV2 RT-PCR SpO_2

All clinical laboratory data will be presented in listings. All continuous laboratory parameters and the change in these parameters at each time points from baseline to end of treatment (Day of discharge) will be summarized using descriptive statistics (n, mean, SD, median and range (Min., Max) overall for the safety population.

Absolute and change from baseline values of laboratory test parameters (Hematology and Serum Biochemistry) will be summarized descriptively by study treatment.

Summary and listing will be prepared for 12 Lead ECG which provides the detailed information of 12 Lead ECG parameters (Heart Rate, PR Interval, RR Interval QRS Interval, QT Interval, QTcF Interval, QTcB interval) and their significance by subjects at screening visit and End of the treatment visit.

Listing will be prepared for Chest X-Ray/CT scan; result of Chest X-Ray/CR scan will provide the significance of abnormality by patients at screening visit.

Listing will be prepared for examinations for SARS CoV2 RT-PCR, SpO_2 and Check for Oxygen support/NIV/MV/ECMO support.

10.4. Vital Signs

Vital signs such as Body Temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, Body Weight and change in these vital signs from baseline to each relevant timepoint will be summarized by treatment for the safety population using descriptive statistics (n, mean, SD, median and range (Min., Max)).

10.5. Physical Examination

Listing will be prepared for Physical Examination which provides the detailed information about the Body Systems (include head, neck, thyroid, eyes, ears, nose, throat, cardiovascular system, Respiratory System, Gastrointestinal System, skin, musculoskeletal, urinary system and genitalia) by subjects at each visit.

10.6. Unscheduled Assessment

Extra assessments (laboratory data, ECG or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the baseline values. If more than one laboratory value is available for a given visit, latest valid assessment at a visit is used for summary and the repeat

assessments will be used for analysis in case if all the assessments are on same date and there is non-missing time, and in case if dates are same and time is missing for some assessments then the average of the assessments will be used as the value for that time point.

10.7. Pharmacokinetic Measurements Analyses

Not applicable.

11. APPENDIX

Appendix : Table of Contents for Data Display Specifications in the separate mock shells file.