BMJ Open

Randomized Double-Blind Placebo Control Trial of Favipiravir in Adults with mild Coronavirus Disease COVID-19

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047495
Article Type:	Protocol
Date Submitted by the Author:	02-Dec-2020
Complete List of Authors:	Bosaeed, Mohammad; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Alharbi, Ahmad ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences hussein, Mohammad ; King Abdullah International Medical Research Center, Biostatistics and Bioinformatics; King Saud bin Abdulaziz University for Health Sciences Abalkhail, Mohammed ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences College of Medicine, Medical Education Sultana, Khizra; King Abdullah International Medical Research Center, Research Office; King Saud bin Abdulaziz University for Health Sciences Musattat, Abrar ; King Abdullah International Medical Research Center, Research Office; King Saud bin Abdulaziz University for Health Sciences Hajar Alqahtani, Hajar Alqahtani; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences, Pharmacy Alshamrani, Majid; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Mahmoud, Ebrahim ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Alothman, Adel ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Alsaedy, Abdulrahman ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Aldibasi, Omar ; King Abdullah International Medical Research Center, Biostatistics and Bioinformatics; King Saud bin Abdulaziz University for Health Sciences Alhagan, Khalid ; King Abdullah International Medical Research Center, Research Trial Services; King Saud bin Abdulaziz University for Health Sciences Asiri, Abdullah ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences, AlJohani, Sameera ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Al-Jeraisy, Majed ; King Abdullah International Medical Research Center, Research Office; King Saud bin Abdulaziz University for Health Sciences Alaskar, Ahmed; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences

Keywords:	VIROLOGY, THERAPEUTICS, COVID-19, Clinical trials < THERAPEUTICS, INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Randomized Double-Blind Placebo Control Trial of Favipiravir in Adults with mild Coronavirus Disease COVID-19

Title Page

1. Mohammad Bosaeed [1,2]
2. Ahmad Alharbi [1,2]
3. Mohammad Hussein[1,2]
4. Mohammed Abalkhail[1,2]
5. Khizra Sultana[1,2]
6. Abrar Musattat[1,2]
7. Hajar Alqahtani[1,2]
8. Majid Alshamrani[1,2]
9. Ebrahim Mahmoud[1,2]
10. Adel Alothman[1,2]
11. Abdulrahman Alsaedy[1,2]
12. Omar Aldibasi[1,2]
13. Khalid Alhagan[1,2]
14. Sameera Aljohani[1,2]
15. Majed Aljeraisy[1,2]
16. Ahmad Alaskar[1,2]

Corresponding Author:
Mohammad Bosaeed,
Consultant, Infectious Diseases.
King Abdulaziz Medical City - Riyadh, Saudi Arabia
Email: dr.bosaeed@live.com
Mobile # +966506706496

Affiliation:
1. King Abdullah International Medical Research Center Riyadh, Kingdom of Saudi Arabia
2. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia

Key Words: Virology, COVID-19, Therapeutics, Clinical Trials, Infectious diseases,

Word Count: 2913

Abstract:

Introduction

A novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed Covid-19 in Dec 2019. There is lack of specific therapeutic agents based on evidence for this novel coronavirus infections; however, several medications have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease the duration of virus carriage to limit the community's transmission.

Methods and Analysis

We hypothesize that mild COVID19 patients treated with Favipiravir will have a shorter duration of time to virus clearance than the control group. Primary outcome is to evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after starting medicine.

Adults (>18 years, Male or non-pregnant female, Diagnosed with Mild COVID-19 within five days of disease onset) are being recruited by physicians participating from the Ministry of National Guard Health Affairs and Ministry of Health ethics committee approved primary health care centers. This double blind randomized trial comprises three significant parts screening, treatment, and follow-up period, where treating physician and patients are blinded. Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a control group (Placebo) with 1800 mg by mouth twice daily for first day, followed by 800mg twice daily for 4-7 days. Serial nasopharyngeal/Oropharyngeal swab samples will be obtained on day 1(-5 days before therapy). On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/ Oropharyngeal PCR COVID19 samples will be requested.

The primary analysis population for evaluating both efficacy and safety outcomes will be a modified ITT population. Anticipating a 10% drop-out rate, we expect to recruit 317 subjects per arm. The results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

Ethics and dissemination

The study was approved by the King Abdullah Medical Research Centre Institutional Review Board and the Ministry of Health Institutional Review Board. Protocol details and any amendments will be reported to https://clinicaltrials.gov/. Results will be published in peer-reviewed journals.

Trial registration number: National Clinical Trial Registry (NCT04464408)

Funding: This study was funded by King Abdullah International Medical Research Centre**.**

Strengths and Limitations

- Double blind randomized placebo controlled trial.
- Large sample size of 576 participants.
- Recruiting is challenging as subjects need to be enrolled within 5 days of disease onset.
- Challenging remote site initiation visit, protocol training and monitoring activities.
- Staff shortage for research due to allocation to other clinical services to address the burden of the pandemic

INTRODUCTION

In December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed Covid-19. The WHO declared the epidemic of COVID-19 as a pandemic on 12th March 2020. (1) According to a recent Chinese study, about 80% of patients present with mild disease, and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years. (2) Mild cases have been found to have viral loads 60-fold less than severe cases. The viral loads of asymptomatic individuals are lower, with possible implications for infectiousness and diagnosis(3) In Saudi Arabia, as of 27th March 2020, 1012 confirmed cases of the disease were reported(4) There are no specific therapeutic agents based on substantial evidence for these novel coronavirus infections; however, several medications have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease the duration of virus carriage to limit the community's transmission.

Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor, has activity against the influenza virus. In addition to its anti-influenza virus activity, favipiravir can block the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses. (4) Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity (5), which theoretically can be active against SARS-CoV-2.

There is an urgent need to explore therapeutic options for SARS-CoV-2 in order to face the pandemic. The selected drug was based on limited evidence clinically and in vitro on the Favipiravir's efficacy in SARS-CoV-2. The medication was listed in many guidelines as a treatment option and ongoing trials assessing its efficacy and safety. Thus, we want to prove the effectiveness of this therapy in treating mild COVID-19 cases.

Research hypothesis

We hypothesize that mild COVID19 patients treated with Favipiravir will have a shorter duration of time to virus clearance than the control group.

METHODS

Study Design

This study is a randomized, , double-blind placebo controlled clinical trial to evaluate novel therapeutic agent's safety and efficacy in adults diagnosed with mild COVID-19. It is a multicenter trial that will compare Favipiravir (experimental arm) to a control arm (Placebo).

Study Population

A convenience sample of adult patients with mild COVID-19 infection identified as positive by PCR confirmed SARS-coV-2 who is eligible at the Ministry of National Guard Health Affairs at Riyadh and Madinah will be assessed for inclusion in the trial. Additionally positive patients visiting the Ministry of Health Institutional Review Board (IRB) and Saudi Food Drug Authority (SFDA) approved primary health care centers in the regions of Riyadh, Makkah and Madinah will also be assessed for eligibility. Figure 1 provides the CONSORT diagram for the trial procedure.

Inclusion Criteria and Exclusion Criteria

Inclusion criteria are: (1) Should be at least 18 years of age, (2) Male or non-pregnant female, (3) Diagnosed with Mild COVID-19* confirmed by positive PCR test for SARS-2-CoV at the time of recruitment, a result within the last five days, (4) Patients have to be enrolled within 5 days of disease onset. Exclusion criteria are (1) Patients with concomitant documented bacterial pneumonia (2) Patients who are pregnant or breastfeeding (3) Known sensitivity/allergy to Favipiravir, (4) Major comorbidities increasing the risk of study drug including: i. Hematologic malignancy, ii. Advanced (stage 4-5) chronic kidney disease or dialysis therapy, Severe liver damage (Child-Pugh score C, AST> 5 times the upper limit), HIV, (5) Gout/history of Gout or hyperuricemia (two times above the ULN), (6) Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug, (7)The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues), (8) Clinical prognostic non-survival, palliative care, or in deep coma and no have response to supportive treatment within three hours of admission.

Definitions:

Mild COVID-19 cases are defined as patient presenting with a mild illness, (absent or mild pneumonia), oxygen saturation >94% at room air; and does not require ICU admission.

Mild illness may include: uncomplicated upper respiratory tract viral infection symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore

throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea, and vomiting.

Viral clearance is defined as polymerase chain reaction (PCR) negative results.

Outcome measurements

Primary outcome

To evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after starting medicine.

Secondary Objectives

- To evaluate Favipiravir's effect on clinical recovery.
- Evaluate symptoms severity and the progression in the disease course in both arms till 28 days after starting medicine.
- To evaluate Favipiravir's effect on the requirement of the use of antipyretics, analgesics, or antibiotics within 15 days after starting medicine.
- To evaluate Favipiravir's effect on disease complications within 28 days after starting medicine (hospitalization, ICU admission or Mechanical ventilation).
- Evaluate the safety of investigational therapeutics as compared to the control arm within 15 days after starting medicine.

Other Variables

Data will also be collected on demographic and epidemiological factors like (age, gender and ethnic group), co-morbidities, vital signs and symptoms at presentation, laboratory findings (CBC, liver function, kidney function ,potassium, sodium, glucose and chest X-ray), any hospitalization during enrollment period and concomitant medications.

Study Procedures

The Study comprises three major parts screening, treatment and follow-up period. Each part consists of specified procedures to be done and assessments to be carried. The investigator and supporting study team will be responsible to document all the procedures and assessments done in the appropriate source document and the patient e-CRFs. All procedures and assessments will support the safety and validity of conclusions drawn from the study protocol. Procedures and assessments such as vital signs, laboratory test, will follow in-house policies and guidelines.

When multiple assessments are taken at the same time point, the most out-of-range value shall be considered. Table 1 describes the different stages of the study and tasks to be completed.

Screening/Baseline

The research coordinator/ principal investigator for the site will check all positive reported COVID-19 by PCR confirmed SARS-coV-2 viral infection in the participating site. An assessment of the eligibility will be performed by the research coordinator against the inclusion/exclusion criteria. The possible study participant can be assessed in the first 72 hours of diagnosis regarding eligibility. Once eligible, informed consent will be obtained.

Randomization

Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a control group (Placebo). Randomization will be stratified by clinical site. The patients will be randomized, utilizing a web based data entry system. The sequence of treatment assignments will be determined before the start of the study. The physician and the participants are blinded to the treatment.

Treatment Period

The treatment intervention would be for a maximum of 7 days from randomization, and it would be as follows: Favipiravir for 7 days: Administer 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily for 4-6 days (Maximum days of therapy is 7 days)

Treatment compliance

Compliance with the study drug will be assessed by the study coordinator at each study visit/ follow up phone call and, he/she will be required to record in the CRF any missed dose, the reason for missing doses, any adverse effect, and any associated issues, beginning from visit 1.

Follow-up Period

The follow- up period would be for 28 days from randomization.

Serial nasopharyngeal/ Oropharyngeal swab samples will be obtained on day 1(-5 days) (before therapy was administered). On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/ Oropharyngeal PCR COVID19 samples requested by the treating team will be recorded.

Patients' follow-up and needed laboratory investigations will be done while the patient is in the hospital. If the patient is discharged or in outpatient settings, the follow up evaluation and

obtaining specimens will be done through a mobile team trained as per study protocol or in an outpatient clinic.

Follow-up of symptoms evaluation should be for 15 days or until patient reaches secondary endpoint (resolving symptoms).

PARTICIPANT DISCONTINUATION

Premature discontinuation of the trial would be based on the decision of DSMB or the investigator initiated based on the following:

- Adverse event: clinical or laboratory event that in the medical judgment of the investigator, for the best interest of the patient are grounds for discontinuation
- A major deviation from the protocol: the patient's findings or conduct failed to adhere to the protocol requirements.
- Other reasons: e.g., an administrative problem such as termination of study by the sponsor.

261

262

263 **Table 1-Flow chart**

	Study period										
											Closeout
Timepoint study days	D1 (-1 Day)	D2	D3	D4	D5	D6	D7	D10	D15	D21	D28
Enrolment and assignment											
Eligibility assessment	x										
Informed consent	x										
Randomization	x										
Baseline data	x										
Study drug administration											
Favipiravir	x	x	x	x	x	x	x				
Adverse effect reaction	x	x	x	x	x	x	x				
Serious adverse event assessment	x	x	x	x	x	x	x	x	x		x
Clinical data collection											
Symptoms evaluation	x	x	x	x	x	x	x	x	x		
Laboratory data collection											
Covid-19 PCR from Respiratory sample *	x				x			x	x		
CBC, renal profile and LFT	x				x			x	x		
ECG	x										

264

265

266

267

STATISTICAL CONSIDERATIONS

General Considerations

This is a randomized, double-blinded study comparing Favipiravir tablets to placebo group to treat subjects with mild SARS-COV-2 infection. The Intention to treat (ITT) analysis will include all subjects randomized. The primary analysis population for evaluating both efficacy and safety outcomes will be a modified ITT population, and include all subjects who have been randomized. The study drug (Favipiravir tablets or Placebo) was started, and the patient did not withdraw consent.

Sample Size and Power Considerations

Assumptions and Study Hypothesis:

a. The current study's primary hypothesis is H0: HR =1 vs. H1: HR ≠1; and HR is the hazard ratio of treatment compared to control arm.

b. Time to viral clearance

In patients with mild COVID19, 90% of the patients clear the virus by day 10 of onset.(1) If we assume an exponential hazard, we estimate the median time of viral clearance in the placebo group to be 8 days.

c. The exact treatment effect from Favipiravir is not known but can be approximated using prior clinical studies. A study comparing Favipiravir's effect to lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral clearance in the Favipiravir arm.(6) To stay on the conservative side, we assume that Favipiravir will reduce the median time to virus clearance to 6 days which is equivalent to hazard ratio of 1.33.

d. We further assume that 90% of the control group patients will have viral clearance within 15 days, and 90% will have viral clearance in the treatment arm.

e. It is anticipated that very few of these subjects will be randomized and not start study treatment (and so be excluded from the primary analysis) or be lost to follow-up (and so have missing data for the primary endpoint). Given certain uncertainties however, we have included a nominal 10% drop out rate.

Sample Size Estimation for Classical Two Arm Parallel Design:

Under the classical two arm parallel design, a one-sided test of whether the hazard ratio is 1 with an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is 1.330. The number of events (i.e., subjects with viral clearance) required to achieve this power is 517.5. The proportions of events during the study are anticipated to be 0.900 for the control group and 0.900 for the treatment group. We anticipate 10% drop out rate and therefore we expect that the trial will recruit 317 subjects per arm. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

The current study will have a single interim analysis, which will occur after the recruitment and follow-up of 40% of the total number of subjects (i.e. 230 subjects). The interim analysis is designed to test for early stopping for futility or efficacy and sample size re-estimation. The interim analysis and final analysis will be based on the sum of the stage wise p-value discussed in Mark and Chang, 2008. The Table 2 describes the interim analysis testing boundaries.

Boundary

Table 2: Interim analysis and sample size Re-estimation

Alpha1 = 0.01	Stop the trial for early efficacy if the interim analysis p-value is less than 0.01
Beta1 =0.25	Stop the trial for futility if the interim analysis P-value is equal to or larger than 0.25
Alpha2=0.1832	Declare the trial significant if the sum of the interim analysis and final stage P-values are less than 0.1832

The sample size re-estimation will be based on the ratio of the planned effect size (1.33) to the observed effect size from the interim analysis according to the following formula:

$$N = \left(\frac{E_0}{E}\right)^a N_0$$

where 'a' is a constant which will be set to 2 and $'N'_0$ is a number chosen to be slightly larger than the classical sample size per group, E_0 is the planned effect size of 1.33, and E is the observed effect size from the interim analysis.

Patient and Public involvement

It was not appropriate or possible to involve patients or the public in the design of the study
The results of the study will be disseminated to the public via social media platforms.

Ethics

This study will be carried out in compliance with the protocol and by the laws and regulations of King Abdullah International medical research Centre ethics committee (KAIMRC IRB). The study will adhere to the principles of Good Clinical Practice that it conforms to a copy of the Declaration of Helsinki. This study was approved by KAIMRC IRB with protocol number RC20/220.The authors will seek approval for protocol amendments, which will be reported to the clinical trials registration site.

CONFIDENTIALITY AND DATAMANAGEMENT

The research coordinator with expertise in data entry will enter data into a password-protected database. Data will be entered and double checked for accuracy. After resolving of any discrepancies and a combination of manual and automated data- review procedures, the final data set will be subject to a quality assurance audit.

A clinical data management review will be performed on all subject data to ensure clinical data quality across all participants and sites. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. Also, the data will be reviewed for adherence to the protocol. During data analysis, non-identifiable data will be provided in a password protected excel sheet.

Data Safety Monitoring Board

A Data and Safety Management Board (DSMB) will be convened to monitor the trial's unblinded data focusing mainly on assuring that the study follows the protocol properly and monitoring the safety issues related to the trial. The DSMB will meet regularly throughout the trial and when AEs trigger study pausing/stopping criteria are triggered.

Discussion

Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase. It acts as a purine analog, which selectively inhibits viral RNA-dependent RNA polymerase (RdRps).

Favipiravir has the characteristic of acting on RNA viruses including, Ebola and Coronaviruses especially, novel coronavirus (2019-nCoV). For the Ebola virus, favipiravir effectively prevented Ebola in mice by 100%, although EC50 (drug concentration was found to reduce viral replication by 50%) ~67 μM. A recent in vitro study on clinical isolates of 2019-nCoV showed that Favipiravir has EC50 =61.88μM.(7)

A study of 80 patients with Covid-19 compared Favipiravir to lopinavir/ritonavir. The study reported a shorter viral clearance time for the Favipiravir arm versus the lopinavir/ritonavir arm median 4 days (IQR: 2.5–9) versus 11days (IQR: 8–13), $P < 0.001$). The Favipiravir arm showed significant chest imaging improvement compared with the lopinavir/ritonavir arm, with an improvement rate of 91.43% versus 62.22% ($P = 0.004$). (6) Furthermore, it was superior to Arbidol in having a higher 7-day clinical recovery rate in patients with Covid-19 and a more significant reduction in the incidence of fever and cough (7). A Japanese observational study assessed the safety and efficacy of favipiravir. The median duration of therapy was 11 days with reported clinical improvement rates at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and 60.3% for mild, moderate, and severe disease, respectively.(8)

According to a study by Jones et al. there are 630 registered trials for COVID 19 on the clinicaltrials.gov website by 1 May 2020. Most of these trials are from Europe, USA, China and other Asian countries. Additionally all the trials on the drugs or biologics (218) are studying drugs like hydroxychloroquine or chloroquine (88), azithromycin (53) and 25 trials assessing convalescent plasma, lopinavir/ ritonavir , stem cell treatments and tocilizumab .(9)

Another study reported 201 trials registered with US registry and WHO clinical trials registry platform. Out of these 93.5% studied drug intervention. From the total trials 49.8% were from

China, 37.8% USA accounting for 87.6% studies from both countries. From the 201 trials only 11 trials are being done on Favipiravir.(10)

As of the 23rd of July, 2020; there are 32 studies registered on clinicaltrials.gov to assess the utility of this drug in the management of COVID-19 (3 completed, 12 recruiting).

(11) Currently there are only two countries (KSA and Kuwait) from Middle East with ongoing trials on Favipiravir with placebo comparator. (12) Our study is the first trial registered from the Middle East region till date funded by the Government of KSA. Recently a study was done in India on Favipiravir in mild to moderate COVID 19 Cases. This was an randomized open label study and the sample size of only 150 patients (13) . There are certain limitations reported in this study which were due to small sample size the hazards ratio reported was small and due to open label nature of the study it may have been subjected to potential bias. The primary endpoint in this study was confounded due to interpretation issues with RT-PCR positivity and its lack of correlation with clinical cure. (13)

Our study it is a double blind; placebo controlled randomized study which provides high quality evidence. The sample size in our study is 576 subjects, which is the largest second to the trial in Kuwait (780) from the presently ongoing trials on Favipiravir.(12) The design of the study eliminates potential bias and the large sample size helps to obtain a hazards ratio of 1.

Limitations:

Numerous challenges are expected during this trial. The trial is ongoing now during restricted travel time, and hospitals restricted nonessential personnel's entry. Protocol training, site initiation visits, and monitoring visits will be performed remotely in many sites. The research team will be assigned to other clinical services, and many members require extra effort. Also, study team member's sicknesses or unprotected exposure to COVID-19 patient strained research resources. Many sites may encounter inadequate supplies of personal protective equipment and trial-related supplies.

Author Contributions:

MoB, AhH, MoA, KhS, AbM, HaQ, MaS, EbM, AdA, AbA, SaA, MaJ, and AhA participated in study design and protocol development. MoB, AbM, KhA, KhS, AbA are involved in subject recruitment and follow-up plan. MoH, OmA, AhA, and MoB participated in the development of statistical analysis plan. KhS, MoB, AbA, and AhH contributed to manuscript preparation. KhS and MoB contributed to review and manuscript submission.

Funding:
This work was supported by King Abdullah International Research Centre, KSA (grant no. RC20/220/R).

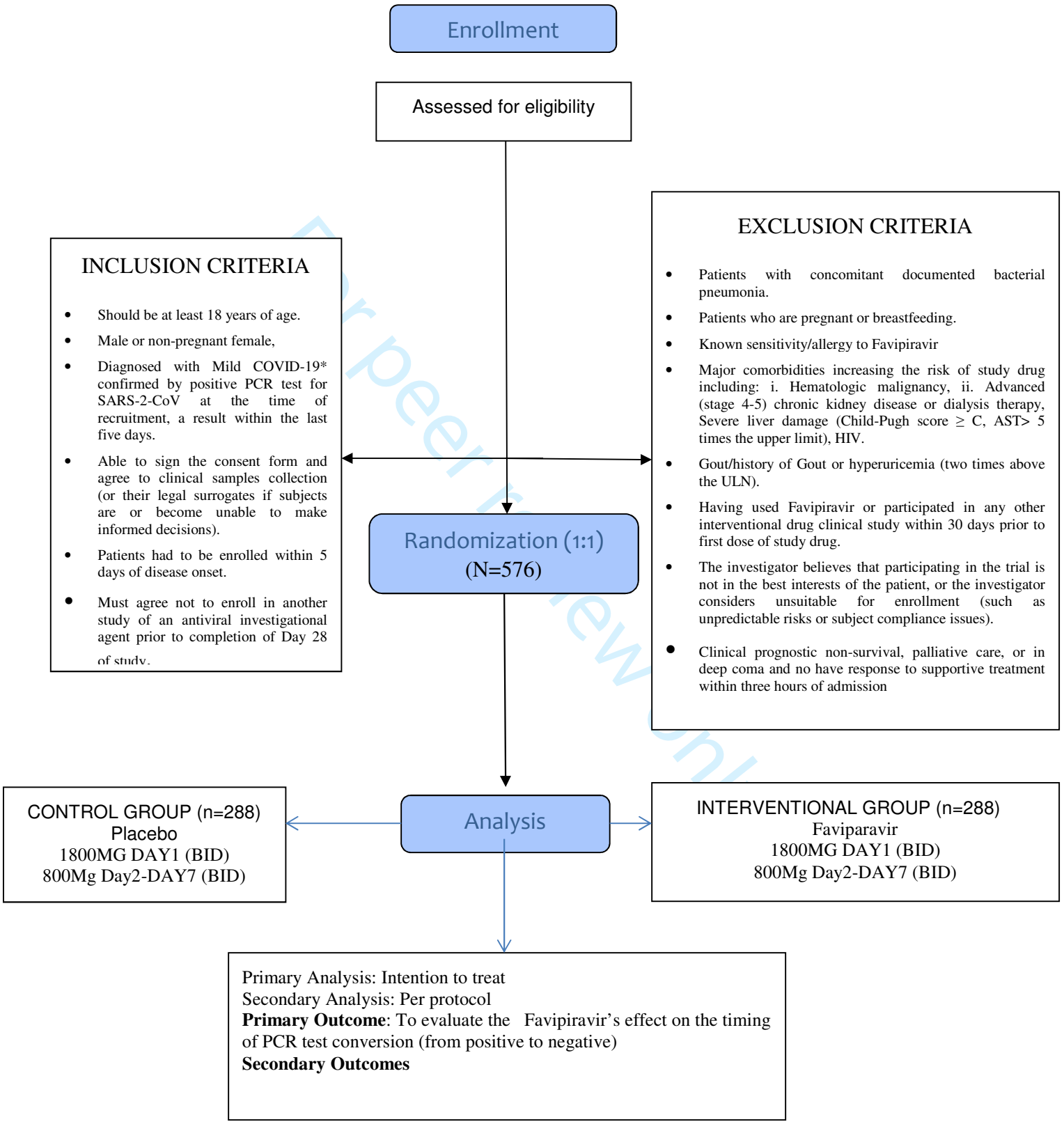
Competing interests:

Authors declare no competing interest.

REFERENCES

1. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. The Lancet Infectious Diseases. 2020;20(6):656-7.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
3. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-94.
4. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral research. 2018;153:85-94.
5. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy Series B, Physical and biological sciences. 2017;93(7):449-63.
6. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing, China). 2020.
7. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020:2020.03.17.20037432.
8. James MI. Preliminary report of favipiravir observational study in Japan released. online: News-Medical.net, 2020.
9. Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered with ClinicalTrials.gov: cross-sectional analysis. BMJ Open. 2020;10(9):e041276.
10. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical trials assessing treatments for COVID-19: a cross-sectional analysis. BMJ Open. 2020;10(6):e039978.
11. Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. Med J Armed Forces India. 2020;76(4):370-6.
12. Listed COVID 19 Studies [Internet]. online: US National Institue of Health (NIH); 2020 [cited 2020 26 Nov]. Clinicaltrials.org]. Available from: https://www.clinicaltrials.gov.
13. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and Safety of Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial. International Journal of Infectious Diseases. 2020.

Figure1. CONSORT reporting of Trials



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3 and 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6 NA
	11b	If relevant, description of the similarity of interventions	10
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A Multicentre Randomized Double-Blinded Placebo-Controlled Trial of Favipiravir in Adults with Mild Coronavirus Disease COVID-19

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047495.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Jan-2021

Complete List of Authors:	Bosaeed, Mohammad; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Alharbi, Ahmad ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences hussein, Mohammad ; King Abdullah International Medical Research Center, Biostatistics and Bioinformatics; King Saud bin Abdulaziz University for Health Sciences Abalkhail, Mohammed ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences College of Medicine, Medical Education Sultana, Khizra; King Abdullah International Medical Research Center, Research Office; King Saud bin Abdulaziz University for Health Sciences Musattat, Abrar ; King Abdullah International Medical Research Center, Research Office; King Saud bin Abdulaziz University for Health Sciences Hajar Alqahtani, Hajar Alqahtani; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences, Pharmacy Alshamrani, Majid; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Mahmoud, Ebrahim ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Alothman, Adel ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Alsaedy, Abdulrahman ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Aldibasi, Omar ; King Abdullah International Medical Research Center, Biostatistics and Bioinformatics; King Saud bin Abdulaziz University for Health Sciences Alhagan, Khalid ; King Abdullah International Medical Research Center, Research Trial Services; King Saud bin Abdulaziz University for Health Sciences Asiri, Abdullah ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences, AlJohani, Sameera ; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences Al-Jeraisy, Majed ; King Abdullah International Medical Research Center, Research Office; King Saud bin Abdulaziz University for Health Sciences Alaskar, Ahmed; King Abdullah International Medical Research Center; King Saud bin Abdulaziz University for Health Sciences

Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Global health
Keywords:	VIROLOGY, THERAPEUTICS, COVID-19, Clinical trials < THERAPEUTICS, INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A Multicentre Randomized Double-Blinded Placebo-Controlled Trial of Favipiravir in Adults with Mild Coronavirus Disease COVID-19

Title Page

1. Mohammad Bosaeed [1,2]
2. Ahmad Alharbi [1,2]
3. Mohammad Hussein[1,2]
4. Mohammed Abalkhail[1,2]
5. Khizra Sultana[1,2]
6. Abrar Musattat[1,2]
7. Hajar Alqahtani[1,2]
8. Majid Alshamrani[1,2]
9. Ebrahim Mahmoud[1,2]
10. Adel Alothman[1,2]
11. Abdulrahman Alsaedy[1,2]
12. Omar Aldibasi[1,2]
13. Khalid Alhagan[1,2]
14. Abdullah Mohammed Asiri[1,2]
15. Sameera Aljohani[1,2]
16. Majed Aljeraisy[1,2]
17. Ahmad Alaskar[1,2]

Corresponding Author:
Mohammad Bosaeed,
Consultant, Infectious Diseases.
King Abdulaziz Medical City - Riyadh, Saudi Arabia
Email: dr.bosaeed@live.com
Mobile # +966506706496

Affiliation:
1. King Abdullah International Medical Research Center Riyadh, Kingdom of Saudi Arabia
2. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia

Key Words: Virology, COVID-19, Therapeutics, Clinical Trials, Infectious diseases,

Word Count: 5160

Abstract:

Introduction

A novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed COVID-19 in Dec 2019. There is a lack of specific therapeutic agents based on evidence for this novel coronavirus infection; however, several medications have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease virus carriage duration to limit the community's transmission..

Methods and Analysis

We hypothesize that mild COVID-19 patients treated with Favipiravir will have a shorter duration of time to virus clearance than the control group. The primary outcome is to evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after starting the medicine.

Adults (>18 years, male or non-pregnant female, diagnosed with mild COVID-19 within five days of disease onset) are being recruited by physicians participating from the Ministry of National Guard Health Affairs(MNGHA) and Ministry of Health(MOH) ethics committee approved primary health care centers. This double-blind, randomized trial comprises three significant parts screening, treatment, and follow-up period, where treating physician and patients are blinded. Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a control group (Placebo) with 1800 mg by mouth twice daily for the first day, followed by 800mg twice daily for 4-7 days. Serial nasopharyngeal/Oropharyngeal swab samples will be obtained on day 1(-5 days before therapy). On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/ Oropharyngeal PCR COVID-19 samples will be requested. The primary analysis population for evaluating both efficacy and safety outcomes will be a modified ITT population. Anticipating a 10% drop-out rate, we expect to recruit 288 subjects per arm. The results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

Ethics and dissemination

The study was approved by the King Abdullah Medical Research Centre Institutional Review Board (28 April 2020) and the Ministry of Health Institutional Review Board (1 July 2020). Protocol details and any amendments will be reported to https://clinicaltrials.gov/ct2/show/NCT04464408. Results will be published in peer-reviewed journals.

Trial registration number: National Clinical Trial Registry (NCT04464408)

Funding: This study was funded by King Abdullah International Medical Research Centre**, Riyadh ,Saudi Arabia**

Strengths and Limitations

- Double blind randomized placebo controlled trial.
- Large sample size of 576 participants.
- Recruiting is challenging as subjects need to be enrolled within 5 days of disease onset.
- Challenging remote site initiation visit, protocol training and monitoring activities.
- Staff shortage for research due to allocation to other clinical services to address the burden of the pandemic

Introduction

In December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed COVID-19. The WHO declared the epidemic of COVID-19 as a pandemic on 12th March 2020. (1) According to a recent Chinese study, "about 80% of patients present with mild disease, and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years". (2) Mild cases have been found to have viral loads 60-fold less than severe cases. The viral loads of asymptomatic individuals are lower, with possible implications for infectiousness and diagnosis. (3) In Saudi Arabia, as of 27th March 2020, 1012 confirmed cases of the disease were reported. (4) There are no specific therapeutic agents based on substantial evidence for these novel coronavirus infections; however, several medications have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease virus carriage duration to limit the community's transmission.

Favipiravir was discovered through the screening of a chemical library for antiviral activity against the influenza virus by the Toyama Chemical Co., Ltd. (5) It was approved for medical use in Japan, in 2014, for the treatment of the new or reemerging pandemic influenza virus infections.(5) In February 2020, favipiravir was also approved for the treatment of novel influenza in China and is further being studied in the Chinese population for experimental treatment of the emergent COVID-19.(6)

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor, has activity against the influenza virus. In addition to its anti-influenza virus activity, favipiravir can block the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses.(4) Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity (7), which theoretically can be active against SARS-CoV-2.

There is an urgent need to explore therapeutic options for SARS-CoV-2 in order to face the pandemic. The selected drug was based on limited evidence clinically and in vitro on the Favipiravir's efficacy in SARS-CoV-2. The medication was listed in many guidelines as a treatment option, and ongoing trials assess its efficacy and safety. (5) Japan, Russia, Saudi Arabia, Thailand, Kenya and India have recommended the usage of favipiravir oral therapy in mild to moderate COVID-19 in the treatment guidelines. (8-13) Thus, we want to prove the effectiveness of this therapy in treating mild COVID-19 cases.

Research hypothesis

We hypothesize that mild COVID-19 patients treated with Favipiravir will have a shorter duration of time to virus clearance than the control group.

Methods and analysis

Study Design

AviMild is a phase III randomized double-blinded placebo-controlled parallel-group multicenter clinical trial to evaluate Favipiravir's safety and efficacy in adults diagnosed with mild COVID-19. The trial involves patients from the community settings from different cities in Saudi Arabia with King Abdullah International Medical Research Center (KAIMRC) as the sponsor. The protocol described in this article is V2.2 approved on 20 Nov 2020. This RCT has been developed according to the Standard Protocol Items: Recommendations for Intervention Trials 2013 statement. (14)

AviMild RCT will compare Favipiravir (experimental arm) to a control arm (Placebo). Patients will be randomly assigned in a 1:1 ratio to both arms. Figure 1 provides an overview of the study design. Any investigational antiviral medication for COVID-19 and other types of antiviral drugs are prohibited. Patients are allowed to continue the medications they were taking before the study, e.g., anti-hypertensive or antidiabetics. The patients are not allowed to participate in other trials as per the study protocol. This is a double-blind study where the treating physician, patients and the research study team are blinded. The trial is registered at the ClinicalTrials.org registry as NCT04464408.

Study Population

A convenience sample of adult patients with mild COVID-19 infection identified as positive by PCR confirmed SARS-CoV -2 from the community. Patients eligible at the Ministry National Guard Health Affairs (MNGHA) at Riyadh and Madinah, Saudi Arabia, will be assessed for inclusion in the trial. Additionally, positive patients visiting the Ministry of Health (MOH) Institutional Review Board (IRB) and Saudi Food Drug Authority (SFDA) approved primary health care centers in the regions of Riyadh, Makkah and Madinah will also be assessed for eligibility. Presently there are seven centers, including the sponsor site. Ministry National Guard Health Affairs (MNGHA) Riyadh, Primary Health Care (PHC)- Mansoura and PHC-Al Urijah

Riyadh, MNGHA Madinah and PHC Safiyah -Madinah, King Fahad Hospital -Madinah, King Abdullah Medical City- Makkah..

The sponsor has subscribed an insurance policy covering the sponsor's own third-party liability as well as the third-party liability of all the investigators involved for the study's duration.

Inclusion Criteria

Patients must be eligible according to the following criteria for enrollment

(1) Should be at least 18 years of age

(2) Male or non-pregnant female (pregnancy testing is not mandatory. If the patient requests or is not sure, the study team will provide it)

(3) Diagnosed with mild COVID-19* confirmed by positive PCR test for SARS-CoV-2 at the time of recruitment, a result within the last five days

(4) Patients have to be enrolled within 5 days of disease onset.

Exclusion criteria

Patients meeting any of the following criteria will be excluded from trial enrolment:

(1) Patients with concomitant documented bacterial pneumonia established through positive sputum cultures

(2) Patients who are pregnant or breastfeeding

(3) Known sensitivity/allergy to Favipiravir (If Faviparavir was used for COVID-19 in the patient previously for influenza)

(4) Major comorbidities increasing the risk of study drug including

- Hematologic malignancy
- Advanced (stage 4-5) chronic kidney disease or dialysis therapy
- Severe liver damage (Child-Pugh score C, AST> 5 times the upper limit)
- HIV
- Gout/history of Gout or hyperuricemia (two times above the ULN)

(6) Having used Favipiravir or participated in any other interventional drug clinical study within 30 days before the first dose of study drug (i.e., the patient received it for influenza previously)

(7) The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues)

(8) Clinical prognostic non-survival, palliative care, or in a deep coma and have no response to supportive treatment within three hours of admission.

(9) Hospitalized patients for moderate or severe COVID-19

Definitions:

a. Mild COVID-19 cases are defined as a patient presenting with a mild illness (absent or mild pneumonia), oxygen saturation >94% at room air, and not requiring ICU admission.

Mild illness may include uncomplicated upper respiratory tract viral infection symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting.

b. Viral clearance is defined as polymerase chain reaction (PCR) negative results.

Randomization

Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a control group (placebo). The randomization list is computer generated and is stratified by clinical site. The patients will be randomized, utilizing an electronic case report (e-CRF) form (REDCAP) to ensure allocation concealment. The sequence of treatment assignments will be determined before the start of the study.

Blinding

The trial is double-blind, meaning that the participants, investigators, and other study staff are unaware of the treatment assignment. The Sponsor's investigational drug unit, not part of the study team holds the information for treatment allocation.

Rationale for study treatment

Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase. It acts as a purine analog, which selectively inhibits viral RNA-dependent RNA polymerase (RdRps).

Favipiravir has the characteristic of acting on RNA viruses, including Ebola and Coronaviruses especially, novel coronavirus. For the Ebola virus, favipiravir effectively prevented Ebola in mice by 100%, although EC50 (drug concentration was found to reduce viral replication by 50%) ~67 μM. A recent in vitro study on clinical isolates of COVID-19 showed that Favipiravir has EC50 =61.88μM. (15)). The dose was chosen based on the drug insert (Fabiflu Prescribing Information) provided for the medication from the studies that were done in Japan and according to the published studies.(13, 16)

Participant Timeline

The study comprises three major parts screening, treatment, and follow-up period. Each part consists of specified procedures to be done and assessments to be carried. The investigator and supporting study team will be responsible for documenting all the procedures and assessments in the appropriate source document and the patient e-CRFs (REDCAP). All procedures and assessments will support the safety and validity of conclusions drawn from the study protocol. Procedures and assessments such as vital signs, laboratory tests will follow in-house policies and guidelines. When multiple assessments are taken for variables such as vital signs or laboratory measurements (e.g., blood pressure), the value that is out of range or abnormal, i.e., higher or lower than the normal range, will be documented. Table 1 and Fig2 describe the time schedule for enrolment, intervention, assessments and visits for participants.

Screening/Baseline: Day -1 to Day1

The site's delegated personnel will check all positive reported COVID-19 by PCR confirmed SARS-CoV-2 viral infection at the participating sites. An assessment of the eligibility will be performed by the delegated personnel against the inclusion/exclusion criteria. The possible study participant can be assessed in the first 72 hours of diagnosis regarding eligibility. Once eligible, informed consent will be obtained. Data will also be collected on demographic and epidemiological factors like (age, gender, and ethnic group), co-morbidities, vital signs and symptoms at presentation, laboratory findings (CBC, liver function, kidney function, potassium, sodium, glucose, and chest X-ray), any hospitalization during the enrollment period and concomitant medications.

Treatment Period: DAY 1

The treatment intervention will be for a maximum of 7 days from randomization, and it would be as follows: Favipiravir for 7 days: Administer 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily for 4-6 or equivalent placebo. The medication and placebo were bought from FujiFilm Toyama Chemical Co. and Zhejiang Hisun Pharmaceutical co., Ltd and it is distributed to all other sites by the sponsor as per enrollment of subjects.

Treatment compliance

Compliance with the study drug will be assessed by the study coordinator at each study visit/ follow up through a phone call. The patient response will be recorded in the e-CRF (Supplementary material 1) for any missed dose, the reason for missing doses, any adverse effect, and any associated issues beginning from visit 1.

Follow-up Period-Day1-15 and Day 28

The follow-up period starts from the second day after randomization for 14 days, where the research coordinator or the physician wills follow-up the patient's health through a phone call. Follow-up of symptoms evaluation should be for 15 days or until the patient reaches the secondary endpoint (resolving symptoms). The patient's assessment will be recorded in the e-CRF. Another follow-up will be made on day 28 days from randomization. On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/ oropharyngeal PCR COVID-19 samples will be requested by delegated specialist trained clinical personnel part of the research team, and results documented in e-CRF. Patients' follow-up and needed laboratory investigations will be done while the patient is in the hospital. If the patient is discharged or in outpatient settings, the follow-up evaluation and obtaining specimens will be done by delegated personnel in the outpatient clinic or mobile team trained as per study protocol.

Table 1-Time points for enrolment, intervention and assessment of outcome measure

	Study period and Follow-up										Closeout
Time point study days	D1 (-1 Day)	D2	D3	D4	D5	D6	D7	D10	D15	D21	D28
Enrolment and assignment-Screening											
Eligibility assessment	X										
Informed consent	X										
Randomization	X										
*Baseline data	X										
Study drug administration-Treatment Period											
Favipiravir or Placebo	x	x	x	x	x	x	x				
Adverse effect reaction	x	x	x	x	x	x	x				
Serious adverse event assessment	x	x	x	x	x	x	x	x	x		x

Clinical data collection											
Symptoms evaluation	x	x	x	x	x	x	x	x	x		
Laboratory data collection											
COVID-19 PCR from Respiratory sample	x				x			x	x		
CBC, renal profile and LFT	x				x			x	x		
ECG	x										

*Baseline data includes the subject's demographics, comorbid conditions, vital signs, symptoms and epidemiological data collected on the day of enrollment.

Outcome measurements: Endpoints selection is based on objectivity and to present the most reliable assessment for a mild infection. Therefore, viral clearance, which captures the viral shedding duration and possible contagiousness period, reflects the best assessment.

Primary outcome

To evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after starting the medicine.

Secondary Objectives

- To evaluate Favipiravir's effect on clinical recovery. This is assessed by evaluating the duration from the start of treatment (Favipiravir or placebo) to the normalization of pyrexia, respiratory symptoms, and relief of cough (or other relevant symptoms at enrollment) that is maintained for at least 72 hours.
- Evaluate symptoms severity and the disease course progression in both arms till 28 days after starting the medicine.
- To evaluate Favipiravir's effect on the requirement of the use of antipyretics, analgesics, or antibiotics within 15 days after starting medicine.
- To evaluate Favipiravir's effect on disease complications within 28 days after starting medicine (hospitalization, ICU admission, or Mechanical ventilation)
- Evaluate the safety of investigational drug compared to the control arm within 15 days after starting the medicine. This is assessed by allergic reactions, medication intolerance, liver toxicity, and hyperuricemia in subjects.

PARTICIPANT DISCONTINUATION

Premature discontinuation of the trial would be based on the decision of the Data Saftey Monitoring Board (DSMB), or the investigator-initiated based on the following:

1. Adverse event: clinical or laboratory event, that in the medical judgment of the investigator, for the best interest of the patient are grounds for discontinuation
2. A major deviation from the protocol: the patient's findings or conduct failed to adhere to the protocol requirements.

Other reasons: e.g., an administrative problem such as termination of study by the sponsor.

Data collection, management and Analysis

The research coordinator with expertise in data entry will enter data into a password-protected database (REDCAP). All observations and other data pertinent to the clinical investigation will be recorded into the e-CRF. Data will be entered and double-checked for accuracy. After resolving any discrepancies and a combination of manual and automated data-review procedures, the final data set will be subject to a quality assurance audit.

A clinical data management review will be performed on all subject data to ensure clinical data quality across all participants and sites. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. Also, the data will be reviewed for adherence to the protocol. During data analysis, non-identifiable data will be provided in a password protected excel sheet. All data are de-identified and coded with a unique number generated by the online data management system REDCAP.

Safety and adverse events monitoring

All adverse events (AE) and serious adverse event (SAE) encountered during the clinical study will be reported on the e-CRF. The information to be entered in the e-CRF will include:

- The time of onset of any AE or the worsening of a previously observed AE
- The specific type of reaction in standard medical terminology
- The duration of the AE (start and stop dates)
- The severity of the adverse event (AE). The severity should be rated as:
    - Mild: discomfort noted, but no disruption of normal daily activity.

- Moderate: discomfort noted of sufficient severity to reduce or adversely affect normal activity.
- Severe: incapacitating, with the inability to work or perform normal daily activity.

- The assessment of the relationship of adverse event (AE) to study medication, i.e., according to the definitions below:
  - Related: with a reasonable causal relationship to the investigational product.
  - Not Related: without a reasonable causal relationship to the investigational product.
  - Other: in such a case, the investigator's causality assessment should be specified.
- Description of action taken in treating the AE and/or change in study medication administration or dose.

As far as possible, all investigators will follow-up participants with AEs until the event is resolved or until, in the investigator's opinion, the event is stabilized or determined to be chronic. Details of AE resolution will be documented in the e-CRF. Any significant changes in AEs will be reported even though the subject has completed the study, including the protocol-required post-treatment follow-up.

Statistical methods:

General Considerations

This is a randomized, double-blinded study comparing Favipiravir tablets to placebo group to treat subjects with mild SARS-CoV-2 infection. The Intention to treat (ITT) analysis will include all subjects randomized which will ignore noncompliance, protocol deviations, withdrawal, and anything that will take place after randomization. (17, 18) The primary analysis population for evaluating both efficacy and safety outcomes will be a modified ITT population, and will include all subjects who have been randomized but will exclude some randomized subjects like patients who were judged ineligible after randomization or patients who withdrew consent or certain patients who never started treatment (17, 18), study drug (Favipiravir tablets or Placebo) was started, and the patient did not withdraw consent. These results assume that the hazard ratio is

constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

Sample Size and Power Considerations

Assumptions and Study Hypothesis:

a. The current study's primary hypothesis is H0: HR =1 vs. H1: HR ≠1; and HR is the hazard ratio of treatment compared to control arm.

b. Time to viral clearance

In patients with mild COVID-19, 90% of the patients clear the virus by day 10 of onset.(1) If we assume an exponential hazard, we estimate the median time of viral clearance in the placebo group to be 8 days.

c. The exact treatment effect from Favipiravir is not known but can be approximated using prior clinical studies. A study comparing Favipiravir's effect to lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral clearance in the Favipiravir arm.(19) To stay on the conservative side, we assume that Favipiravir will reduce the median time to virus clearance to 6 days which is equivalent to hazard ratio of 1.33.

d. We further assume that 90% of the control group patients will have viral clearance within 15 days, and 90% will have viral clearance in the treatment arm. It is anticipated that very few of these subjects will be randomized and not start study treatment (and so be excluded from the primary analysis) or be lost to follow-up (and so have missing data for the primary endpoint). Given certain uncertainties however, we have included a nominal 10% drop out rate.

Sample Size Estimation for Classical Two Arm Parallel Design:

Under the classical two-arm parallel design, a one-sided test of whether the hazard ratio is 1 with an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is 1.330.

The sample size re-estimation will be based on the ratio of the planned effect size (1.33) to the observed effect size from the interim analysis according to the following formula:

$$N = \left(\frac{E_0}{E}\right)^a N_0$$

where 'a' is a constant which will be set to 2 and is a number chosen to be slightly larger than the classical sample size per group, is the planned effect size of 1.33, and E is the observed effect size from the interim analysis.

A detailed statistical analysis plan will be developed before undertaking any comparative analyses of outcomes. The following provides a summary of the approach to analysis for the primary endpoint**.**

Analysis of the primary endpoint:

The primary endpoint of the current study is the rate of viral clearance. The number and percent of subjects who met the endpoint by day 15 of follow up will be calculated and tabulated. Due to the nature of the data collection (i.e., subjects clearance will be observed during specific follow-up time), survival analysis methods for interval-censored data will be used to analyze the data. All results will be reported in H.R and the corresponding lower confidence limit and one-sided p-value.

For secondary endpoints:

- Quantitative variables such as 'change from baseline in clinical scores' are expected to have reasonably skewed distributions. They may be subject to censoring, e.g., for subjects in hospital on day 28, compared between randomized arms using non-parametric tests (Wilcoxon's test).
- Analysis of the other secondary endpoints will use a proportional odds model with an indicator variable for randomized treatment. The Wald test will generate a p-value comparing treatments and the estimated proportional odds ratio comparing treatments with associated 95% CI.
- Analysis of AE data will primarily be descriptive based on MedDRA coding of events. The proportion of subjects experiencing an SAE and the proportion experiencing a Grade
- Three or higher AEs will be compared between randomized arms using Fisher's Exact Test.

For enrolled subjects who were not randomized (i.e., screen failures) or randomized but did not receive the treatment, the final analysis will detail safety (deaths and SAEs) and reasons they were not randomized or did not receive treatment, respectively.

Data Monitoring:

This committee will be independent of the sponsor with relevant therapeutic and biostatistical experience to allow for the ongoing review of data from this trial. A Data and Safety Management Board (DSMB) will be convened to monitor the trial's unblinded data focusing mainly on assuring that the study follows the protocol correctly and monitoring the safety issues related to the trial. The DSMB will meet when AEs trigger study pausing/stopping criteria are triggered. The DSMB has no competing interests.

The current study will have a single interim analysis, which will occur after the recruitment and follow-up of 40% of the total number of subjects (i.e., 230 subjects). The interim analysis is designed to test for early stopping for futility or efficacy and sample size re-estimation.(20) The interim analysis and final analysis will be based on the sum of the stage-wise p-value . Table 2 describes the interim analysis testing boundaries.

Table 2: Interim analysis and sample size Re-estimation

Alpha1 = 0.01	Stop the trial for early efficacy if the interim analysis p-value is less than 0.01
Beta1 =0.25	Stop the trial for futility if the interim analysis P-value is equal to or larger than 0.25
Alpha2=0.1832	Declare the trial significant if the sum of the interim analysis and final stage P-values are less than 0.1832

Frequency and procedures for auditing trial conduct:

The investigator will allow representatives of the regulatory authorities (Saudi Food & Drugs Authority) to conduct an audit anytime they request it. The regulatory authorities are independent from the sponsor.

Ethics

This study will be carried out in compliance with the protocol and by the laws and regulations of King Abdullah International Medical Research Centre Ethics Committee (KAIMRC IRB) and the Ministry of Health Ethics Committee (MOH IRB). The date for approval for the first version was 28 April 2020, and for the protocol version, V2.2 is 25 November 2020. KAIMRC IRB approved this study with protocol number RC20/220. The study applies the principles established in the Declaration of Helsinki. The participants will sign a written informed consent form (ICF-supplementary material 2) before the first assessment and data collection by delegated personnel. Contact details of the principal investigator are provided to the patients for queries and concerns. Patients are free to withdraw from the study at any time without any consequences regarding their standard clinical care. Any change or addition to this protocol requires a written amendment approved by the sponsor and the investigators. Before implementation, the investigators will transmit all major amendments to the Ethics Committees, examining the initial protocol. The investigators will transmit a copy of the Ethics Committee's opinion to the sponsor. The investigators will notify all minor amendments to the Ethics Committee that had examined the initial protocol. All amendments will be reported to the clinical trials registration site.

Discussion

During the Ebola virus disease outbreak, the JIKI trial illustrated an improved survival rate in patients with moderate to high viral load with favipiravir. (21) Similarly, Bai et al.'s study proved a significant decline in viral load with favipiravir in patients with moderate viral load at baseline. (22) These findings support the role of favipiravir in viral load reduction. Since the homology of gene sequences of SARS-CoV-2 and SARS was over 90%, it is expected that the intervention of antiviral drugs in COVID-19 patients will likely improve or shorten the time to viral clearance. (23) The reduction in time to viral clearance is chosen as the endpoint based on the above evidence. Therefore, viral clearance, which captures the viral shedding duration and possible contagiousness period, reflects the best assessment. Several published trials have studied similar endpoints as our study due to their clinical significance. A study of 80 patients with COVID-19 compared Favipiravir to lopinavir/ritonavir. The study reported a shorter viral clearance time for the Favipiravir arm versus the lopinavir/ritonavir arm median 4 days (IQR: 2.5–9) versus 11days (IQR: 8–13), $P < 0.001$). Multivariable Cox regression showed that favipiravir was significantly ($p = 0.026$) associated with faster viral clearance. Additionally the

timing of antiviral therapy reached near significance (p = 0.055). (19) Furthermore, it was superior to Arbidol in having a higher 7-day clinical recovery rate in patients with COVID-19 and a more significant reduction in fever and cough (15). A Japanese observational study assessed the safety and efficacy of favipiravir. The median duration of therapy was 11 days, with reported clinical improvement rates at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and 60.3% for mild, moderate, and severe disease, respectively. (24) A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19 chose the primary endpoint was viral clearance by day 6. The secondary endpoint was a change in viral load by day 6. Additionally, exploratory endpoints included time to defervescence and resolution of symptoms. (25) A trial from Russia enrolled 60 patients (40 on favipiravir and 20 on Supportive Care) with primary endpoint as viral elimination. The secondary endpoints were defervescence and RT-PCR negativity. (13) Lately, a phase 3, open-label, randomized, multicenter study (Glenmark Pharmaceuticals) was initiated in India. The primary endpoint was time until the cessation of oral shedding of the SARS-CoV-2 virus. (26)

According to a study by Jones et al., there are 630 registered trials for COVID-19 on the clinicaltrials.gov website by 1 May, 2020. Most of these trials are from Europe, the USA, China, and other Asian countries. Additionally, all the trials on the drugs or biologics (218) are studying drugs like hydroxychloroquine or chloroquine (88), azithromycin (53), and 25 trials assessing convalescent plasma, lopinavir/ ritonavir, stem cell treatments, and tocilizumab. (27)

Another study reported 201 trials registered with the US registry and WHO clinical trials registry platform. Out of these, 93.5% studied drug intervention. From the total trials, 49.8% were from China, 37.8% USA accounting for 87.6% of both countries studies. From the 201 trials, only 11 trials are being done on Favipiravir. (28) As of 23 July 2020, there are 32 studies registered on clinicaltrials.gov to assess this drug's utility in the management of COVID-19 (3 completed, 12 recruiting). (29)

Many clinical trials conducted in China, Japan, Russia, and India had an open-label design, which leads to reporting biased results. (13, 19, 25, 26) Recently a study was done in India on Favipiravir in mild to moderate COVID-19 Cases. This was a randomized, open-label study and the sample size of only 150 patients. (30) There are certain limitations reported in this study, which were due to the small sample size. The hazard ratio reported was small, and due to the

study's open-label nature, it may have been subjected to potential bias. This study's primary endpoint was confounded due to interpretation issues with RT-PCR positivity and its lack of correlation with the clinical cure. (30)

A systemic review and meta-analysis of Favipiravir reported evidence showing potential benefits of this drug in clinical and imaging improvement after treating COVID-19 patients. Therefore there is a need for additional randomized, double-blind clinical trials to form a definite opinion about the rationale to use this drug. There were several drawbacks to the studies that have already been published, such as non-randomized design, small sample sizes, and different durations of treatment, different dosage regimes, and lack of blinding. (31)

In our study, we adopted the design double-blind, placebo-controlled randomized study, which provides the best evidence of causation. (32) Randomized double-blind placebo control studies (RDPCS) are regarded as the "gold standard" of epidemiologic studies. They are employed to illustrate superiority, equivalence, and non-inferiority. Well-designed RDPCS gives the most robust possible evidence of causation. The benefits of randomization are 1. It avoids selection bias that may happen if either the physician or the patient decides the treatment, 2. It removes most confounding by all known and unknown factors as it prevents an association between the treatment and any other known or unknown factor. Blinding with randomization evades reporting bias as no one is aware of the treatment; hence all treatment groups will be treated the same. The use of placebo as control leads to the placebo effect where the person on placebo will think that they are taking the actual treatment, which leads them to feel better or respond to it due to wishful thinking. The presence of placebo control will help to compare the drug's effectiveness against the placebo's effectiveness (33-35)

There are currently only two countries (KSA and Kuwait) from the Middle East with ongoing Favipiravir trials with a placebo comparator. (29) Our study is the first trial registered from the Middle East region to date funded by the government of KSA. Our study's sample size is 576 subjects, the second largest to Kuwait's trial (780) from the presently ongoing Favipiravir trials.(29) .

Limitations:

Numerous challenges are expected during this trial. The trial is ongoing now during restricted travel time, and hospitals restricted nonessential personnel's entry. Protocol training, site

initiation visits, and monitoring visits will be performed remotely in many sites. The research team will be assigned to other clinical services, and many members require extra effort. Also, study team member's sicknesses or unprotected exposure to COVID-19 patient strained research resources. Many sites may encounter inadequate supplies of personal protective equipment and trial-related supplies. The study is prone to certain biases due to the design, such as non-compliance, withdrawals after randomization, and attrition/losses to follow-up.

Trial status

This trial began on 23 July 2020. On 27 Jan 2021, 160 patients have been included.

Data sharing plan

Study protocol and statistical plan will be openly available.

Acknowledgements

We acknowledge principal investigators for all sites (alphabetical order): Ali Tolba, Hanan Turkistany, Mohannad Bahlaq, Saad Alshahrani, Sanaa Al Rehily, Zied Ghaifer Ali. We thank all staff involved in data monitoring.

Author Contributions:

MoB, AhH, MoA, KhS, AbM, HaQ, MaS, EbM, AdA, AbA, SaA, MaJ, and AhA participated in study design and protocol development. MoB, AbM, KhA, KhS, AbA are involved in subject recruitment and follow-up plan. MoH, OmA, AhA, and MoB participated in the development of statistical analysis plan. KhS, MoB, AbA, and AhH contributed to manuscript preparation. KhS and MoB contributed to review and manuscript submission.

Funding:
This trial was funded by King Abdullah International Research Centre, KSA (grant no. RC20/220/R).

Competing interests:
Authors declare no competing interest.

Patient and Public involvement

This research was done without patient and public involvement due to time constraints. The results of the study will be disseminated to the public via social media platforms.

Figure 1 Overview of Study

Figure 2 Schedule of Enrollment

REFERENCES

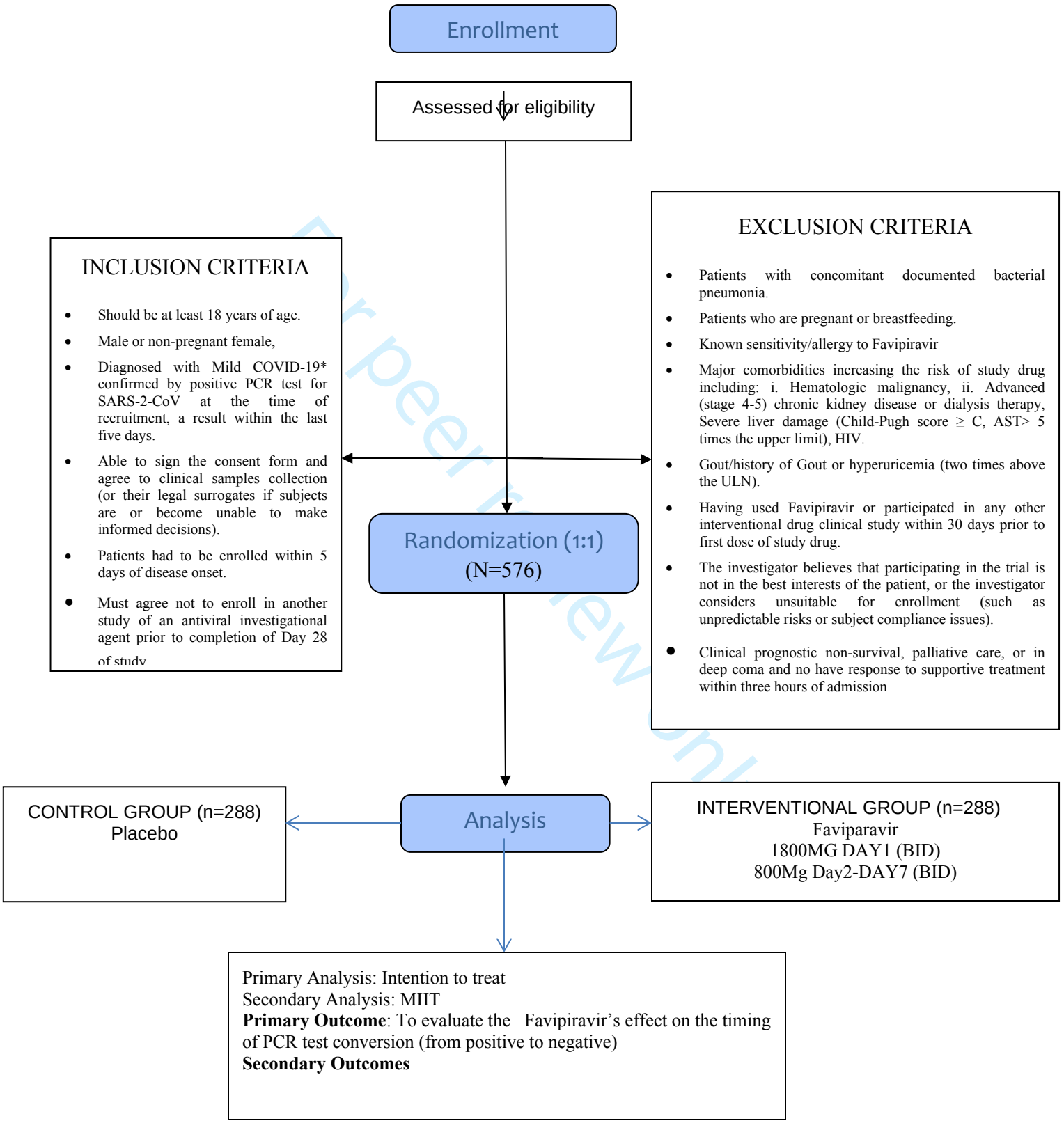
1. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. The Lancet Infectious Diseases. 2020;20(6):656-7.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
3. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-94.
4. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral research. 2018;153:85-94.
5. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacology & therapeutics. 2020;209:107512.
6. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews Drug discovery. 2020;19(3):149-50.
7. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy Series B, Physical and biological sciences. 2017;93(7):449-63.
8. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) [Internet]. online: Centre For Disease Control and Prevention; 2020 [updated Dec 8,2020; cited 2021 18 Jan]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
9. COVID-19. Coronavirus Disease Guidelines [online]. Kingdom of Saudi Arabia: Ministry of Health; 2020 [cited 2021 18 Jan]. Available from: https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx.
10. Compendium of Guidelines,Instruction and Standard Operative Procedures for Covid-19 [Internet]. India: Medical Education and Drugs Department Government of Maharashtra; 2020 [cited 2021 18 Jan]. 4:[Available from: https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volume%204.pdf.
11. Ratanarat R, Sivakorn C, Viarasilpa T, Schultz MJ. Critical Care Management of Patients with COVID-19: Early Experience in Thailand. Am J Trop Med Hyg. 2020;103(1):48-54.
12. Interim guidelines. Prevention, diagnostics and treatment of a new coronavirus infection (COVID-19) [Internet]. Russia: MOH of the Russian Federation; 2020 [updated 28 April 2020; cited 2021 18 Jan]. 6:[Available from: https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf.

13. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases. 2021;102:501-8.
14. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Annals of Internal Medicine. 2013;158(3):200-7.
15. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020:2020.03.17.20037432.
16. Favipiravir: Report on the Deliberation Results;. 2014. Japan: Toyama Chemical, Evaluation and Licensing Division PaFSBMoH, Labour and Welfare; 2014 March 4 Report No.
17. Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. The Medical journal of Australia. 2003;179(8):438-40.
18. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res. 2011;2(3):109-12.
19. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing, China). 2020.
20. Kumar A, Chakraborty BS. Interim analysis: A rational approach of decision making in clinical trial. J Adv Pharm Technol Res. 2016;7(4):118-22.
21. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. PLoS medicine. 2016;13(3):e1001967.
22. Bai CQ, Mu JS, Kargbo D, Song YB, Niu WK, Nie WM, et al. Clinical and Virological Characteristics of Ebola Virus Disease Patients Treated With Favipiravir (T-705)-Sierra Leone, 2014. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(10):1288-94.
23. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727-33.
24. James MI. Preliminary report of favipiravir observational study in Japan released. online: News-Medical.net, 2020.
25. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19. Antimicrobial Agents and Chemotherapy. 2020;64(12):e01897-20.
26. Singh P. A Clinical Study on Favipiravir Compared to Standard Supportive Care in Patients With Mild to Moderate COVID-19 [Online]. Cochrane COVID-19 Study Register2020 [updated April]. Version 3 [Available from: ICTRP (http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43504).
27. Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered with ClinicalTrials.gov: cross-sectional analysis. BMJ Open. 2020;10(9):e041276.
28. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical trials assessing treatments for COVID-19: a cross-sectional analysis. BMJ Open. 2020;10(6):e039978.
29. Listed COVID 19 Studies [Internet]. online: US National Institue of Health (NIH); 2020 [cited 2020 26 Nov]. Clinicaltrials.org]. Available from: https://www.clinicaltrials.gov.
30. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and Safety of Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial. International Journal of Infectious Diseases. 2020.
31. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. Virology journal. 2020;17(1):141.
32. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ. 2000;321(7256):255-6.
33. Oleckno WA. Essential Epidemiology: Principles and Applications. 4180 IL route 83, suite 101 Long Groove, IL: Waveland Press, Inc.; 2002.

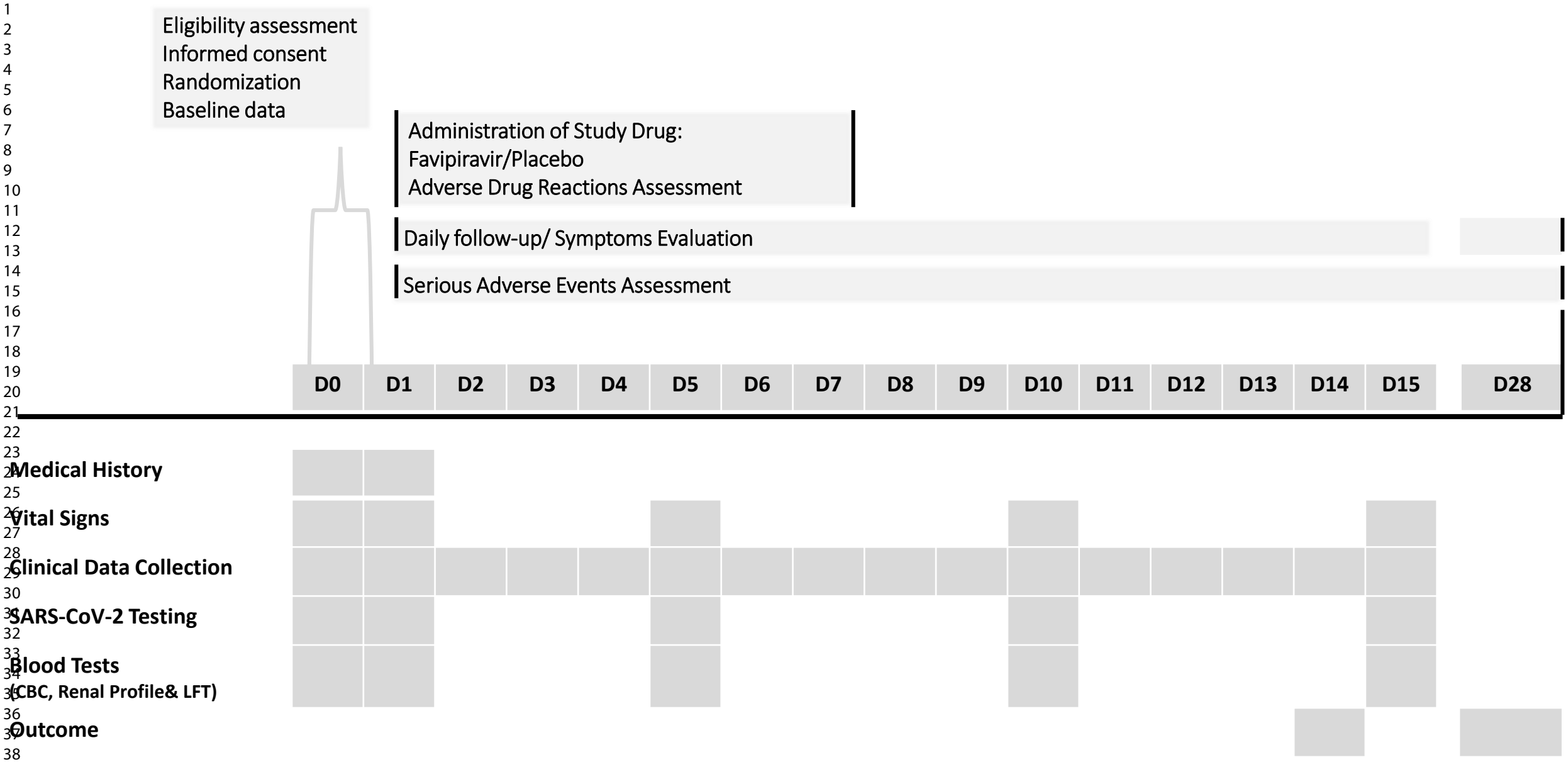
34. Hulley S, Cummings S, Browner W, Grady D, Newman T. Designing clinical research. 503 Walnut street, Philadelphia, PA, USA: Williams and Wilkins .A Walters Kluwer business Lippincot; 2007.

35. Manja V, Lakshminrusimha S. Epidemiology and Clinical Research Design, Part 1: Study Types. Neoreviews. 2014;15(12):e558-e69.

Fig1: AviMild arms. BID, two times per day; MIIT, modified intention to treat



Enrollment Process in AVI-Mild19 Clinical Trial



Demographics And Epidemiological Factors

Record ID	_____
Demographics	
Subject ID	_____
Patient Initial	_____
Date of Birth	_____
Age	_____ (year)
Enrolment date	_____
Ethnic group	◯ Arab ◯ Non Arab
Nationality	_____
Gender	◯ Male ◯ Female
Epidemiological Factors	
1.Close contact* with a confirmed or probable case of COVID-19 infection, while that patient was symptomatic	◯ Yes ◯ No ◯ Unknown
2.Presence in a healthcare facility where COVID-19 infections have been managed	◯ Yes ◯ No ◯ Unknown
3.Presence in a laboratory handling suspected or confirmed COVID-19 samples	◯ Yes ◯ No ◯ Unknown

Clinical Inclusion And Exclusion Criteria

Inclusion Criteria	
1.Male or non-pregnant female	◯ Yes ◯ No
2.Diagnosed with Mild COVID-19 by Positive PCR confirmed SARS-coV-2 all the time of recruitment	◯ Yes ◯ No
3.Able to sign the consent form and agree to clinical samples collection (or their legal surrogates if subjects are or become unable to make informed decisions).	◯ Yes ◯ No
4.Patient enrolled within 5 days of disease onset	◯ Yes ◯ No
5.Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study.	◯ Yes ◯ No
Exclusion Criteria	
1.Patients with concomitant documented bacterial pneumonia	◯ Yes ◯ No
2. Patients who are pregnant or breastfeeding	◯ Yes ◯ No
3. Known sensitivity/allergy to Favipiravir	◯ Yes ◯ No
4. Major comorbidities increasing the risk of study drug including: i. Hematologic malignancy, ii. Advanced (stage 4-5) chronic kidney disease or dialysis therapy, Severe liver damage (Child-Pugh score ≥ C, AST> 5 times the upper limit), HIV.	◯ Yes ◯ No
5. Gout/history of Gout or hyperuricemia (two times above the ULN)	◯ Yes ◯ No
6.Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug.	◯ Yes ◯ No

7.The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues)	◯ Yes ◯ No
8.Clinical prognostic non-survival, palliative care, or in deep coma and have no response to supportive treatment within three hours of admission	◯ Yes ◯ No
Randomization	
Site	◯ Site1 ◯ Site2 ◯ Site3 ◯ Site4 ◯ Site5 ◯ Site6 ◯ Site7 ◯ Site8 ◯ Site9 ◯ Site10
Patient Recruited in ?	◯ Hospital ◯ Community
Treatment	◯ A ◯ B ◯ C ◯ D
Randomization Time	_____

Co-Morbidities

Height

_____ (cm)

Weight

_____ (kg)

Co-morbidities and risk factors - Charlson Index will be calculated for each patient at analysis.

	Yes	No	NA
Hypertension	○	○	○
Chronic cardiac disease, including congenital heart disease (not hypertension)	○	○	○
Chronic pulmonary disease (not asthma)	○	○	○
Asthma (physician diagnosed)	○	○	○
Chronic kidney disease	○	○	○
Chronic liver disease	○	○	○
Chronic neurological disorder	○	○	○
Chronic Rheumatologic/Auto-immune disorder	○	○	○
Obesity (BMI more than 30)	○	○	○
Diabetes with complications	○	○	○
Diabetes without complications	○	○	○
Smoking	○	○	○
Other	○	○	○

Specify, Other Co-Morbidities

_____

Onset And Admission

At Other Facility

Onset date of first/earliest symptom	_____
Did the patient visit another health care facility since the onset date of first/earliest symptom?	◯ Yes ◯ No ◯ NA
Date of the visit	_____
Name of Facility	_____
City	_____
What health care was provided?	◯ Inpatient (Ward, ICU) ◯ Outpatient (ER, Clinic, Primary Care) ◯ NA ◯ Others
Was admission required?	◯ Yes ◯ No ◯ NA
Date of Admission	_____
Date of Discharge	_____

At This Facility

Location of Patient at the Time of Randomization	◯ Outpatient ◯ ER ◯ Ward
Was Admission Required?	◯ Yes ◯ No ◯ NA
Admission Date at this Facility	_____

Vital Signs At Randomization

(First Available Data at Presentation/Admission-within 24 Hours)	
Temperature	_____ (°C)
Heart Rate	_____ (Beats Per Minute)
Respiratory Rate	_____ (Breaths Per Minute)
Systolic BP	_____ (mmHg)
Diastolic BP	_____ (mmHg)
Oxygen Saturation:	_____ (%)
Oxygen saturation On:	◯ Room air ◯ Oxygen therapy ◯ NA
Specify Therapy	◯ Nasal Cannula ◯ Facemask ◯ Non- rebreathable mask ◯ High flow nasal cannula ◯ Non-invasive ventilation (BiPap, CPap) ◯ Invasive Mechanical Ventilation
Please, mention amount	_____
	◯ L/min ◯ %

Symptoms

Observed/reported at admission and associated with this episode of acute illness			
	Yes	No	NA
Fever	○	○	○
Cough	○	○	○
Cough with Sputum Production	○	○	○
Cough with Bloody Sputum/Haemoptysis	○	○	○
Sore Throat	○	○	○
Runny Nose (Rhinorrhoea)	○	○	○
Chest Pain	○	○	○
Shortness of Breath (Dyspnea)	○	○	○
Loss of smell	○	○	○
Loss of taste	○	○	○
Abdominal Pain	○	○	○
Vomiting / Nausea	○	○	○
Diarrhoea	○	○	○
Ear Pain	○	○	○
Muscle Aches (Myalgia)	○	○	○
Joint Pain (Arthralgia)	○	○	○
Fatigue / Malaise	○	○	○
Lower Chest Wall Indrawing	○	○	○
Headache	○	○	○
Conjunctivitis	○	○	○
Skin Rash	○	○	○
Skin Ulcers	○	○	○
Lymphadenopathy	○	○	○

Daily Clinical Assesment

Complete one form on admission, one form on admission to ICU, and daily up to 28 days or until discharge or death if earlier. Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A')

Study Day (clinical assesment study day start on 2nd day after randomization)	_____ (Day)
Date of Phone Assesment	_____
Time	_____
Current admission to ICU?	◯ Yes ◯ No
FiO2 (0.21-1.0)	_____
SaO2	_____ (%)
PaO2 at time of FiO2 above	_____
	◯ kPa ◯ mmHg
PaO2 sample type:	◯ Arterial ◯ Venous ◯ Capillary ◯ N/A
From same blood gas record as PaO2	_____
	◯ kPa ◯ mmHg
pH	_____
HCO3	_____ (mEq/L)

Systolic Blood Pressure	_____ (mmHg)
Diastolic Blood Pressure	_____ (mmHg)
Mean Arterial Blood Pressure	_____ (mmHg)
Urine flow rate	_____ (mL/24 hoursCheck if estimated)
Glasgow Coma Score (GCS / 15)	_____

Is the patient currently receiving, or has received (between 00:00 to 24:00 on day of assessment) (apply to all questions in this section):

	Yes	No	N/A
Non-invasive ventilation (e.g. BIPAP, CPAP)	◯	◯	◯
Invasive ventilation	◯	◯	◯
Extra corporeal life support (ECLS)	◯	◯	◯
High-flow nasal cannula oxygen therapy	◯	◯	◯
Dialysis/Hemofiltration	◯	◯	◯
Any vasopressor/inotropic support	◯	◯	◯

Progress of Symptoms at 1st Presentation(pyrexia, short of breath, and relief of cough and/or others) Can stop recording if resolved for 72 hours

◯ Worsening
◯ Same
◯ Better
◯ Resolved

Signs and Symptoms

New signs and symptoms	◯ Yes ◯ No
Specify,	_____ (L/min)
Starting Date	_____
Fever	◯ Yes, ◯ No

Fever Result	_____ (°C)
Any hospital/ER visits	◯ Yes ◯ No
Was Vital Signs Collected?	◯ Yes ◯ No
Temperature	_____ (°C)
Heart Rate	_____ (Beat Per Minut)
Respiratory Rate	_____ (Breath Per Minute)
Systolic Blood Pressure	_____ (mmHg)
Diastolic Blood Pressure	_____ (mmHg)
Oxygen Saturation	_____ (%)
Oxygen On	◯ Room air ◯ Oxygen therapy ◯ NA
Specify, Oxygen Therapy	_____

SARS-2-COV Testing

Sample study day	◯ Day 1(-5 day) ◯ Day 5 (+/- 1 day) ◯ Day 10 (+/-1 day) ◯ Day 15 (+/- 2 day)
Collection Date	_____
Biospecimen Type	◯ Nasopharyngeal swab ◯ Oropharyngeal swab ◯ Combined Nasopharyngeal and Oropharyngeal swab ◯ Sputum ◯ BAL
Laboratory labResult	◯ Positive ◯ Negative ◯ NA

Lab Assessment Form

Complete one form on admission, one form on admission to ICU, and daily up to 28 days or until discharge or death if earlier. Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A')

Study Day

- ◯ Day 1 (+1 day)
- ◯ Day 5 (±1 day)
- ◯ Day 10 (±1 day)
- ◯ Day 15 (±2 day)

Laboratory Assessement

Haemoglobin

_____

◯ g/L ◯ g/dL

WBC Count

_____

◯ x109/L ◯ x103/µL

Lymphocyte count

_____
(cells/ µL)

Neutrophil count

_____
(cells/ µL)

Platelets

_____

◯ x109/L ◯ x103/µL

ALT/SGPT

_____
(U/L)

Total Bilirubin

_____

◯ µmol/L ◯ mg/dL

AST/SGOT

_____
(U/L)

Glucose

_____

	◯ mmol/L ◯ mg/dL
Blood Urea Nitrogen (urea)	_____
	◯ mmol/L ◯ mg/dL
	◯ mmol/L ◯ mg/dL
Creatinine	_____
	◯ umol/L ◯ mg/dL
Sodium	_____ (mEq/L)
Potassium	_____ (mEq/L)
Chest X-Ray performed?	◯ Yes ◯ No ◯ NA
Were Infiltrates Present?	◯ Yes-Unilateral ◯ Yes - Bilateral ◯ No ◯ NA
.	
ECG performed?	◯ Yes ◯ No ◯ N/A
if YES QT Interval	_____

Daily Study Drug

Favipiravir / Placebo	
Was Favipiravir given?	◯ Yes ◯ No
Dose	_____
Dose Number	_____
Date	_____
Time given	_____
Drug Method	◯ Syrup ◯ tablet

Pathogen Testing

Was Other pathogen testing done during this illness episode?	◯ Yes ◯ No ◯ NA
Bacteria	◯ Yes - confirmed ◯ No
What Bacteria?	_____
Other Infectious Respiratory Diagnosis	◯ Yes- Confirmed ◯ Yes- Probable ◯ No
Specify, Other Infectious Respiratory Diagnosis	_____
If None of the Above , Suspected Non-Infective	◯ Yes ◯ No

Complication (At day 28)

At any time during hospitalization did the patient experience:	Yes	No
Pulmonary Embolism	○	○
Bacterial Pneumonia	○	○
Coagulopathy	○	○
Acute lung Injury/ARDS	○	○
Anemia	○	○
Pneumothorax	○	○
Pleural Effusion	○	○
Acute renal Injury/Failure	○	○
Seizure	○	○
Congestive Heart Failure	○	○
Meningitis/ Encephalitis	○	○
Stroke/Cerebrovascular Accident	○	○
Endocarditis / Myocarditis / Pericarditis	○	○
Cardiac Arrhythmia	○	○
Bacteremia	○	○
Cardiac Arrest	○	○
Liver Dysfunction	○	○
Rhabdomyolysis / Myositis	○	○
Other	○	○

Specify other Complication _____

Treatment

At any time during enrollment did the patient receive/undergo?	
Hospital admission?	◯ YES ◯ NO ◯ N/A
date of hospital admission	_____
date of hospital discharge	_____
ICU or High Dependency Unit Admission?	◯ Yes ◯ No ◯ NA
Date of ICU Admission	_____
Date of ICU Discharge	_____
Oxygen Therapy?	◯ Yes ◯ No ◯ NA
Specify therapy	_____
Non-invasive Ventilation? (e.g. BIPAP, CPAP)	◯ Yes ◯ No ◯ NA
Invasive Ventilation (Any)?	◯ Yes ◯ No ◯ NA
Total Duration	_____ (Days)
Tracheostomy Inserted	◯ Yes ◯ No ◯ NA
ECMO?	◯ Yes ◯ No ◯ NA
Renal Replacement Therapy (RRT) or Dialysis?	◯ Yes ◯ No ◯ NA
Inotropes/Vasopressors?	◯ Yes ◯ No ◯ NA
First/Start Date	_____

Last/End Date	
OTHER Intervention or Procedure	

Medication

Antiviral Agent?	◯ Yes ◯ No ◯ NA
Specify, Antiviral Agent	☐ Favipiravir ☐ Hydroxychloroquine ☐ chloroquine ☐ Lopinavir/Ritonavir ☐ Azithromycin ☐ Interferon ☐ Oseltamivir
Favipiravir Dose	_____
Favipiravir_ start date	_____
Favipiravir_ end date	_____
Hydroxychloroquine Dose	_____
Hydroxychloroquine_Start date	_____
Hydroxychloroquine_End date	_____
Chloroquine Dose	_____
Chloroquine _Start date	_____
Chloroquine _End date	_____
Lopinavir/Ritonavir Dose	_____
Lopinavir/Ritonavir_Start Date	_____
Lopinavir/Ritonavir_End Date	_____
Azithromycin Dose	_____
Azithromycin_Start date	_____

Azithromycin_end date	_____
Interferon Dose	_____
Interferon_Start date	_____
Interferon_End date	_____
Oseltamivir Dose	_____
Oseltamivir_Start date	_____
Oseltamivir_End date	_____
Anti-Interleukin-6 Agents?	◯ Yes ◯ No
Please ,Provide Type	_____
Please ,Provide the Dose	_____
Antibiotic?	◯ Yes ◯ No ◯ NA
Dose	_____
Type	_____
Is the patient take another antibiotic?	◯ Yes ◯ No ◯ NA
Antibiotic_2 Type	_____
Antibiotic_2 Dose	_____
Antibiotic_3 Type	_____
Antibiotic_3 Dose	_____

Antibiotic_4 Type	_____
Antibiotic_4 Dose	_____
Convalescent plasma?	◯ Yes ◯ No ◯ N/A
Specify	_____
Corticosteriod?	◯ Yes ◯ No
Dose	_____
Type	_____
Duration	_____

Outcome

Outcome at Day 14	
Outcome at day 14:	☐ Alive ☐ Hospitalization ☐ Transfer to other facility ☐ Death ☐ Unknown
Outcome Date	_____
Hospital Discharge Date	_____
Outcome at Day 28	
Outcome at Day 28	◯ Alive ◯ Death
Outcome Date	_____

Adverse Drug Reaction

Allergic Reaction	
Day	_____
Skin Rash/Urticaria	◯ No ◯ 1 ◯ 2 ◯ 3
Bronchospasm	◯ No ◯ 1 ◯ 2 ◯ 3
Dyspnea	◯ No ◯ 1 ◯ 2 ◯ 3
Tongue Edema	◯ No ◯ 1 ◯ 2 ◯ 3
Local Skin Necrosis at the Injection Site	◯ No ◯ 1 ◯ 2 ◯ 3
OtherI	◯ No ◯ 1 ◯ 2 ◯ 3
Specify,	_____
OtherII	◯ No ◯ 1 ◯ 2 ◯ 3
Specify,	_____
Gastrointestinal	
Diarrhea	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Dysgeusia	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Nausea	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Vomiting	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Abdominal Pain	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5

OtherI	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____
OtherII	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____

Central Nervous System

Headache	◯ No ◯ 1 ◯ 2 ◯ 3
Insomnia	◯ No ◯ 1 ◯ 2 ◯ 3
Psychosis	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Depression	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Mania	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
ECG: QT Interval Changes	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
OtherI	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____
OtherII	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____

Kingdom of Saudi Arabia
Ministry of National Guard - Health Affairs

المملكة العربية السعودية
وزارة الحرس الوطني – الشؤون الصحية

Informed Consent for Research Study – Interventional Studies

Study Title	:	**A Trial of Favipiravir in Adults with Mild Coronavirus Disease Covid-19**
Study No.	:	
ICF version and date:		**V2, 15/09/2020**
Principal Investigator	:	**Dr. Mohammad Bosaeed**
Sponsor	:	**King Abdullah International Medical Research Center (KAIMRC)**
Principal Investigator Address	:	**King Abdulaziz Medical City- Riyadh Department of Medicine (MC 1443) P. O. Box 22490 Riyadh 11426 +966(0)18011111 Ext. 17535. bosaeedmo@ngha.med.sa**

1. Introduction:

- You are being invited to take part voluntarily in a research study because you have a mild COVID-19 infection. We are studying an antiviral medication called FAVIPARAVIR. This antiviral drug is approved in other countries like Japan to be used for influenza virus. We want to study its effect on the COVID-19 infection. Many countries like USA, Japan Italy and India are doing similar studies to see the effect of this antiviral medication in decreasing the illness caused due to COVID-19 infection.

- Please take time to read this information carefully. Discuss it with any one you want for the right advice (This may include a friend, a relative or a family doctor).

2. Study Purpose:

- This is a research study. The purpose of this study is to measure the effect of this medication on time of viral shedding and the resolution of symptoms like tiredness and lack of energy, fever, cough, and shortness of breath, sore throat, nasal congestion, vomiting, diarrhea etc. This study will also measure how safe this medication is to be used in treating COVID19 infection.

3. Duration of Participation:

- If you agree to participate in the trial, you will be required to take the medication for maximum period of 7 days. You will be followed up every day for 14 days to monitor your condition. We will also check on you on day 28 for a follow up on your well-being.

4. Number of Subjects participating/ study Area and settings:

- In this research study 576 patients like you will be participating. This study will be conducted in King Abdulaziz Medical City -Riyadh and other hospitals across the Kingdom.

5. Study Procedures:

- You will be put in a group randomly (like flipping a coin) to antiviral Favipiravir or the Placebo group (these are pills that look like Faviparavir but they have no effect on your body or your infection.)
- You will receive Favipiravir (AVIGAN) or placebo 1800mg i.e. 9 tablets on the 1st day two times in a day, then from next day till day 7 the dose will change to 800mg i.e. 4 tablets, two times by mouth.

- You will have a 50% chance of receiving either the medication Faviparavir or placebo.

Patient responsibility:

- You will need to record all the doses of the medication you will take at home in the given medication log
- If you miss a dose ,please record it as missed dose
- At the end of 7 days, please kindly bring back the empty bottle or the bottle with missed pills. Also bring the medication log you used to record the pills you took.
- You will need to come back to your study doctor on the day 5, 10 and 15 counting from the day you signed this consent and we will collect blood samples with a swab from your throat, nose or a sputum sample.

6. When will my participation end?

You will take this medication for a maximum of 7 days only. We will follow-up with you every day to check on your health for 14 days. We will check again on day 28 to know your well-being.

7. Risks and inconveniences:

- Like with all other medications this medication can also have some side effects that are common. These include increase in uric acid levels, diarrhea, abnormal liver tests and decrease in neutrophil count(neutrophils are type of white blood cells in your body that help to fight infection)
- Some people might have an allergic reaction to any of the ingredients of this medication.
- As you are required to give blood for lab tests on day 5, 10 and 15, the blood draw can cause bruising or pain at the site of blood draw. In some people this can cause fainting and rarely there can be infection at the site of blood draw
- Pregnant women will not be enrolled in this study. Male participants are advised to use the most effective contraceptive method during their participation and 7 days after the treatment ends. **Complication**: If pregnancy took place when you were taking this medication, information from animal studies showed that this medication spreads to sperm and cause the death of embryo or cause growing defects in embryos.
- There might be unknown reactions that can take place that we do not know yet.
- You will be informed with any new information that becomes available and this may affect your desire to start or continue the study.

8. Important information regarding females participation in the study:

If you are pregnant or suspect pregnancy, please inform us, as we cannot include pregnant or

suspected pregnant females in this study.

9. Costs and compensation for participation in this study:

You will not receive any compensation for your participation in this trial. However, in the event of an illness or injury related to the study medication, all treating procedures, follow-ups, hospitalization, will be provided to you immediately.

10. Benefits:

Previous studies done in USA and JAPAN have shown that this medication had a positive effect in treating influenza virus.

You may or may not benefit directly from participating in this research, but your participation may help other patients with COVID-19.

This research study will increase the medical knowledge which will help to decide if FAVAPIRAVIR medication can be used in treatment of COVID-19 in the future.

11. Alternative Treatment(s):

You will be receiving the routine treatment as per the treating physicians during the course of the study and you will be made aware of any new treatment available for the disease.

12. Information about participation:

Your participation in this study is totally voluntary, you have the right to withdraw at any time you want without mentioning the reasons. If you do not want to take part, you will receive standard care provided by your doctor, and your decision about the study will not affect your current or future medical care.

The study doctor and the study sponsor have the right to withdraw you from the study if he decided that it's better for your medical condition. Or you did not comply with study requirements.

If you have any other diseases or adverse events the principal investigator will decide whether to continue with participation in the study or not.

13. Confidentiality and Authorization to collect, use and disclose Personal Medical Information:

All information related to you including personal and medical data provided and collected by the study doctor and recorded in the study records will be handled as confidential and no one except authorized research team at King Abdullah International Medical Research Center (KAIMRC), Sponsors, Institutional Review Board (IRB), Research Scientific Committee (RC), Ministry of Health auditors, the Saudi Food and Drug Administration (SFDA) and related personnel that can have access to record, review and analyze them.

All the information collected in subjects records belong to King Abdullah International Medical Research Center. In case any results of the study are published, your personal information will never be mentioned, it may be coded in symbols known for research team

14. Communication

In case of any research related inquiries or medical care during study, or any injuries, emergency cases feel free to contact the study principal investigator **Dr. Mohammad Bosaeed** through Phone number: **+966(0)18011111 Ext. 17535.**
In case you have enquiries related to your rights as a research subject you can contact the Institutional Review Board on Tel. **0114294432** or **011429376**

- I've been given the opportunity to discuss my questions about participating in this study and the research team has answered all my questions, if I have any further questions I will call **Dr. Mohammad Bosaeed**

- I understand that my participation in this research is voluntary and I know that I have the right to withdraw when I decide without affecting the medical care that I receive usually and also understand that the principal investigator has the right end my participation as it deems appropriate to me.

- And I also understand that non-compliance with research procedures and/or the visits dates might end my participation of this study.

- I understand that every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

- By signing this informed consent form I acknowledged that I did not give up any of my legal rights, also I confirm that I have received a sufficient information about the study and that I have read and understood the information in this informed consent form and I have had the opportunity to discuss the study and ask questions and have been satisfied with the received explanations.

- I understand that after signing this informed consent form I will receive a signed and dated copy.
- By signing and dating this informed consent form, I agree to participate in this research study.

Subject Name	**Signature**	**Date**
Name of the legal guardian Type if the patient is minor (less than 18 years)	**Signature**	**Date**
Name of the witness Type if the subject agrees verbally and he/she is illiterate	**Signature**	**Date**
Name of the Principal Investigator	**Signature**	**Date**
Person who discussed the consent	**Signature**	**Date**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	3

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	3
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol:A Multicentre Randomized Double-Blinded Placebo-Controlled Trial of Favipiravir in Adults with Mild Coronavirus Disease COVID-19

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047495.R2
Article Type:	Protocol
Date Submitted by the Author:	03-Mar-2021
Complete List of Authors:	Bosaeed, Mohammad; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Alharbi, Ahmad ; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine hussein, Mohammad ; King Abdullah International Medical Research Center, Biostatistics and Bioinformatics Abalkhail, Mohammed ; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences Sultana, Khizra; King Abdullah International Medical Research Center, Clinical Trial Services; King Saud bin Abdulaziz University for Health Sciences Musattat, Abrar ; King Abdullah International Medical Research Center, Clinical Trial Services; King Saud bin Abdulaziz University for Health Sciences Hajar Alqahtani, Hajar Alqahtani; Ministry of National Guard Health Affairs, Department of Pharmaceutical care ; King Saud bin Abdulaziz University for Health Sciences Alshamrani, Majid; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Mahmoud, Ebrahim ; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Alothman, Adel ; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Alsaedy, Abdulrahman ; Ministry of National Guard Health Affairs, Department of Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Aldibasi, Omar ; King Abdullah International Medical Research Center, Biostatistics and Bioinformatics; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Alhagan, Khalid ; King Abdullah International Medical Research Center, Clinical Trial Services; King Saud bin Abdulaziz University for Health Sciences Asiri, Abdullah ; Ministry of National Guard Health Affairs, Department of

	Nursing; King Saud bin Abdulaziz University for Health Sciences, AlJohani, Sameera ; Ministry of National Guard Health Affairs, Department of Pathology and Laboratory Medicine; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Al-Jeraisy, Majed ; King Abdullah International Medical Research Center, Clinical Trial Services; King Saud bin Abdulaziz University for Health Sciences, College of Medicine Alaskar, Ahmed; Ministry of National Guard Health Affairs, Department of Oncology; King Saud bin Abdulaziz University for Health Sciences, College of Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Global health
Keywords:	VIROLOGY, THERAPEUTICS, COVID-19, Clinical trials < THERAPEUTICS, INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Protocol: A Multicentre Randomized Double-Blinded Placebo-Controlled Trial of Favipiravir in Adults with Mild Coronavirus Disease COVID-19

TITLE PAGE

1. Mohammad Bosaeed [1,3,9]
2. Ahmad Alharbi [1,9]
3. Mohammad Hussein[2]
4. Mohammed Abalkhail[1]
5. Khizra Sultana[3,9]
6. Abrar Musattat[3,9]
7. Hajar Alqahtani[4]
8. Majid Alshamrani[1,9]
9. Ebrahim Mahmoud[1,9]
10. Adel Alothman[1,9]
11. Abdulrahman Alsaedy[1,9]
12. Omar Aldibasi[2,9]
13. Khalid Alhagan[3]
14. Abdullah Mohammed Asiri[5]
15. Sameera Aljohani[6,9]
16. Majed Aljeraisy[3,4]
17. Ahmad Alaskar[7,8,9]

CORRESPONDING AUTHOR

Mohammad Bosaeed,
Consultant, Infectious Diseases.
King Abdulaziz Medical City - Riyadh,
Department of Medicine (MC1443)
P.O. Box 22490 Riyadh 11426
Kingdom of Saudi Arabia
Email: dr.bosaeed@live.com

AFFILIATION

1. Department of Medicine, Ministry of National Guard health Affairs (MNGHA), Riyadh, Kingdom of Saudi Arabia
2. Department of Biostatistics, King Abdullah International Medical Research Centre (KAIMRC), Riyadh, Kingdom of Saudi Arabia
3. Clinical Trials services, King Abdullah International Medical Research Centre (KAIMRC), Riyadh, Kingdom of Saudi Arabia
4. Department of Pharmaceutical care Ministry of National Guard health Affairs (MNGHA), Riyadh, Kingdom of Saudi Arabia
5. Department of Nursing, Ministry of National Guard health Affairs (MNGHA), Riyadh, Kingdom of Saudi Arabia

6. Department of Pathology and Laboratory Medicine, Ministry of National Guard health Affairs (MNGHA), Riyadh, Kingdom of Saudi Arabia
7. Department of Oncology, Ministry of National Guard health Affairs (MNGHA), Riyadh, Kingdom of Saudi Arabia
8. King Abdullah International Medical Research Center (KAIMRC), Riyadh, Kingdom of Saudi Arabia
9. College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Kingdom of Saudi Arabia

WORD COUNT: 5160

Key Words: Virology, COVID-19, Therapeutics, Clinical Trials, Infectious diseases,

ABSTRACT

Introduction

A novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed COVID-19 in Dec 2019. There is a lack of specific therapeutic agents based on evidence for this novel coronavirus infection; however, several medications have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease virus carriage duration to limit the community's transmission.

Methods and Analysis

We hypothesize that mild COVID-19 patients treated with Favipiravir will have a shorter duration of time to virus clearance than the control group. The primary outcome is to evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after starting the medicine.

Adults (>18 years, male or non-pregnant female, diagnosed with mild COVID-19 within five days of disease onset) are being recruited by physicians participating from the Ministry of National Guard Health Affairs(MNGHA) and Ministry of Health(MOH) ethics committee approved primary health care centers. This double-blind, randomized trial comprises three significant parts screening, treatment, and follow-up period, where treating physician and patients are blinded. Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a control group (Placebo) with 1800 mg by mouth twice daily for the first day, followed by 800mg twice daily for 4-7 days. Serial nasopharyngeal/Oropharyngeal swab samples will be obtained on day 1(-5 days before therapy). On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/ Oropharyngeal PCR COVID-19 samples will be requested.

The primary analysis population for evaluating both efficacy and safety outcomes will be a modified ITT population. Anticipating a 10% drop-out rate, we expect to recruit 288 subjects per arm. The results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

Ethics and dissemination

The study was approved by the King Abdullah Medical Research Centre Institutional Review Board (28 April 2020) and the Ministry of Health Institutional Review Board (1 July 2020). Protocol details and any amendments will be reported to https://clinicaltrials.gov/ct2/show/NCT04464408. Results will be published in peer-reviewed journals.

Trial registration number: National Clinical Trial Registry (NCT04464408)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Double blind randomized placebo controlled trial.
- Large sample size of 576 participants.
- Recruiting is challenging as subjects need to be enrolled within 5 days of disease onset.
- Challenging remote site initiation visit, protocol training and monitoring activities.
- Staff shortage for research due to allocation to other clinical services to address the burden of the pandemic

INTRODUCTION

In December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of respiratory illness termed COVID-19. The WHO declared the epidemic of COVID-19 as a pandemic on 12th March 2020. (1) According to a recent Chinese study, "about 80% of patients present with mild disease, and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years". (2) Mild cases have been found to have viral loads 60-fold less than severe cases. The viral loads of asymptomatic individuals are lower, with possible implications for infectiousness and diagnosis.(2) In Saudi Arabia, as of 25th Feb 202, 376,000 confirmed cases of the disease were reported.(3) There are no specific therapeutic agents based on substantial evidence for these novel coronavirus infections; however, several medications have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease virus carriage duration to limit the community's transmission.

Favipiravir was discovered through the screening of a chemical library for antiviral activity against the influenza virus by the Toyama Chemical Co., Ltd. (4) It was approved for medical use in Japan, in 2014, for the treatment of the new or reemerging pandemic influenza virus infections.(4) In February 2020, favipiravir was also approved for the treatment of novel influenza in China and is further being studied in the Chinese population for experimental treatment of the emergent COVID-19.(5)

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor, has activity against the influenza virus. In addition to its anti-influenza virus activity, favipiravir can block the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses.(6) Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity (7), which theoretically can be active against SARS-CoV-2.

There is an urgent need to explore therapeutic options for SARS-CoV-2 in order to face the pandemic. The selected drug was based on limited evidence clinically and in vitro on the Favipiravir's efficacy in SARS-CoV-2. The medication was listed in many guidelines as a treatment option, and ongoing trials assess its efficacy and safety. (4) Japan, Russia, Saudi Arabia, Thailand, Kenya and India have recommended the usage of favipiravir oral therapy in

mild to moderate COVID-19 in the treatment guidelines. (8-13) Thus, we want to prove the effectiveness of this therapy in treating mild COVID-19 cases.

Research Hypothesis

We hypothesize that mild COVID-19 patients treated with Favipiravir will have a shorter duration of time to virus clearance than the control group.

METHODS AND ANALYSIS

Study Design

AviMild is a phase III randomized double-blinded placebo-controlled parallel-group multicenter clinical trial to evaluate Favipiravir's safety and efficacy in adults diagnosed with mild COVID-19. The trial involves patients from the community settings from different cities in Saudi Arabia with King Abdullah International Medical Research Center (KAIMRC) as the sponsor. The protocol described in this article is V2.2 approved on 20 Nov 2020. This RCT has been developed according to the Standard Protocol Items: Recommendations for Intervention Trials 2013 statement. (14)

AviMild RCT will compare Favipiravir (experimental arm) to a control arm (Placebo). Patients will be randomly assigned in a 1:1 ratio to both arms. Figure 1 provides an overview of the study design. Any investigational antiviral medication for COVID-19 and other types of antiviral drugs are prohibited. Patients are allowed to continue the medications they were taking before the study, e.g., anti-hypertensive or antidiabetics. The patients are not allowed to participate in other trials as per the study protocol. This is a double-blind study where the treating physician and patients are blinded. The study's recruitment start date was 23 July 2020, and it will continue till reaching the sample size or up to Dec 2021. The trial is registered at the ClinicalTrials.org registry as NCT04464408.

Study Population

A convenience sample of adult patients with mild COVID-19 infection identified as positive by PCR confirmed SARS-CoV -2 from the community. Patients eligible at the Ministry National Guard Health Affairs (MNGHA) at Riyadh and Madinah, Saudi Arabia, will be assessed for inclusion in the trial. Additionally, positive patients visiting the Ministry of Health (MOH) Institutional Review Board (IRB) and Saudi Food Drug Authority (SFDA) approved primary health care centers in the regions of Riyadh, Makkah and Madinah will also be assessed for eligibility. Presently there are seven centers, including the sponsor site. Ministry National Guard

Health Affairs (MNGHA) Riyadh, Primary Health Care (PHC)- Mansoura and PHC-Al Urijah Riyadh, MNGHA Madinah and PHC Safiyah -Madinah, King Fahad Hospital -Madinah, King Abdullah Medical City- Makkah..

The sponsor has subscribed an insurance policy covering the sponsor's own third-party liability as well as the third-party liability of all the investigators involved for the study's duration.

Inclusion Criteria

Patients must be eligible according to the following criteria for enrollment

(1) Should be at least 18 years of age

(2) Male or non-pregnant female (pregnancy testing is not mandatory. If the patient requests or is not sure, the study team will provide it)

(3) Diagnosed with mild COVID-19* confirmed by positive PCR test for SARS-CoV-2 at the time of recruitment, a result within the last five days

(4) Patients have to be enrolled within 5 days of disease onset.

Exclusion criteria

Patients meeting any of the following criteria will be excluded from trial enrolment:

(1) Patients with concomitant documented bacterial pneumonia established through positive sputum cultures

(2) Patients who are pregnant or breastfeeding

(3) Known sensitivity/allergy to Favipiravir (If Faviparavir was used for COVID-19 in the patient previously for influenza)

(4) Major comorbidities increasing the risk of study drug including

- Hematologic malignancy
- Advanced (stage 4-5) chronic kidney disease or dialysis therapy
- Severe liver damage (Child-Pugh score C, AST> 5 times the upper limit)
- HIV
- Gout/history of Gout or hyperuricemia (two times above the ULN)

(6) Having used Favipiravir or participated in any other interventional drug clinical study within 30 days before the first dose of study drug (i.e., the patient received it for influenza previously)

(7) The investigator believes that participating in the trial is not in the best interests of the

patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues)

(8) Clinical prognostic non-survival, palliative care, or in a deep coma and have no response to supportive treatment within three hours of admission.

(9) Hospitalized patients for moderate or severe COVID-19

Definitions:

a. Mild COVID-19 cases are defined as a patient presenting with a mild illness (absent or mild pneumonia), oxygen saturation >94% at room air, and not requiring ICU admission.

Mild illness may include uncomplicated upper respiratory tract viral infection symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting.

b. Viral clearance is defined as polymerase chain reaction (PCR) negative results.

Randomization

Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a control group (placebo). The randomization list is computer generated and is stratified by clinical site. The patients will be randomized, utilizing an electronic case report (e-CRF) form (REDCAP) to ensure allocation concealment. The sequence of treatment assignments will be determined before the start of the study.

Blinding

The trial is double-blind, meaning that the participants, investigators, and other study staff are unaware of the treatment assignment. The Sponsor's investigational drug unit, not part of the study team holds the information for treatment allocation.

RATIONALE FOR STUDY TREATMENT

Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase. It acts as a purine analog, which selectively inhibits viral RNA-dependent RNA polymerase (RdRps).

Favipiravir has the characteristic of acting on RNA viruses, including Ebola and Coronaviruses especially, novel coronavirus. For the Ebola virus, favipiravir effectively prevented Ebola in mice by 100%, although EC50 (drug concentration was found to reduce viral replication by 50%) ~67 μM. A recent in vitro study on clinical isolates of COVID-19 showed that Favipiravir has EC50 =61.88μM. (15)). The dose was chosen based on the drug insert (Fabiflu Prescribing

Information) provided for the medication from the studies that were done in Japan and according to the published studies.(13, 16)

Participant Timeline

The study comprises three major parts screening, treatment, and follow-up period. Each part consists of specified procedures to be done and assessments to be carried. The investigator and supporting study team will be responsible for documenting all the procedures and assessments in the appropriate source document and the patient e-CRFs (REDCAP). All procedures and assessments will support the safety and validity of conclusions drawn from the study protocol. Procedures and assessments such as vital signs, laboratory tests will follow in-house policies and guidelines. When multiple assessments are taken for variables such as vital signs or laboratory measurements (e.g., blood pressure), the value that is out of range or abnormal, i.e., higher or lower than the normal range, will be documented. Table 1 and Fig2 describe the time schedule for enrolment, intervention, assessments and visits for participants.

Screening/Baseline: Day -1 to Day1

The site's delegated personnel will check all positive reported COVID-19 by PCR confirmed SARS-CoV-2 viral infection at the participating sites. An assessment of the eligibility will be performed by the delegated personnel against the inclusion/exclusion criteria. The possible study participant can be assessed in the first 72 hours of diagnosis regarding eligibility. Once eligible, informed consent will be obtained. Data will also be collected on demographic and epidemiological factors like (age, gender, and ethnic group), co-morbidities, vital signs and symptoms at presentation, laboratory findings (CBC, liver function, kidney function, potassium, sodium, glucose, and chest X-ray), any hospitalization during the enrollment period and concomitant medications.

Treatment Period: DAY 1

The treatment intervention will be for a maximum of 7 days from randomization, and it would be as follows: Favipiravir for 7 days: Administer 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily for 4-6 or equivalent placebo. The medication and placebo were bought from FujiFilm Toyama Chemical Co. and Zhejiang Hisun

Pharmaceutical co., Ltd and it is distributed to all other sites by the sponsor as per enrollment of subjects.

Treatment compliance

Compliance with the study drug will be assessed by the study coordinator at each study visit/ follow up through a phone call. The patient response will be recorded in the e-CRF (Supplementary material 1) for any missed dose, the reason for missing doses, any adverse effect, and any associated issues beginning from visit 1.

Follow-up Period-Day1-15 and Day 28

The follow-up period starts from the second day after randomization for 14 days, where the research coordinator or the physician wills follow-up the patient's health through a phone call. Follow-up of symptoms evaluation should be for 15 days or until the patient reaches the secondary endpoint (resolving symptoms). The patient's assessment will be recorded in the e-CRF. Another follow-up will be made on day 28 days from randomization. On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/ oropharyngeal PCR COVID-19 samples will be requested by delegated specialist trained clinical personnel part of the research team, and results documented in e-CRF. Patients' follow-up and needed laboratory investigations will be done while the patient is in the hospital. If the patient is discharged or in outpatient settings, the follow-up evaluation and obtaining specimens will be done by delegated personnel in the outpatient clinic or mobile team trained as per study protocol.

Table 1-Time points for enrolment, intervention and assessment of outcome measure

	Study period and Follow-up										Closeout
Time point study days	D1 (-1 Day)	D2	D3	D4	D5	D6	D7	D10	D15	D21	D28
Enrolment and assignment-Screening											
Eligibility assessment	X										
Informed consent	X										
Randomization	X										
*Baseline data	X										
Study drug administration-Treatment Period											
Favipiravir or Placebo	x	x	x	x	x	x	x				

Adverse effect reaction	x	x	x	x	x	x	x				
Serious adverse event assessment	x	x	x	x	x	x	x	x	x		x
Clinical data collection											
Symptoms evaluation	x	x	x	x	x	x	x	x	x		
Laboratory data collection											
COVID-19 PCR from Respiratory sample	x				x			x	x		
CBC, renal profile and LFT	x				x			x	x		
ECG	x										

*Baseline data includes the subject's demographics, comorbid conditions, vital signs, symptoms and epidemiological data collected on the day of enrollment.

OUTCOME MEASUREMENTS

Endpoints selection is based on objectivity and to present the most reliable assessment for a mild infection. Therefore, viral clearance, which captures the viral shedding duration and possible contagiousness period, reflects the best assessment.

Primary outcome

To evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after starting the medicine.

Secondary Outcome

- To evaluate Favipiravir's effect on clinical recovery. This is assessed by evaluating the duration from the start of treatment (Favipiravir or placebo) to the normalization of pyrexia, respiratory symptoms, and relief of cough (or other relevant symptoms at enrollment) that is maintained for at least 72 hours.
- Evaluate symptoms severity and the disease course progression in both arms till 28 days after starting the medicine.
- To evaluate Favipiravir's effect on the requirement of the use of antipyretics, analgesics, or antibiotics within 15 days after starting medicine.
- To evaluate Favipiravir's effect on disease complications within 28 days after starting medicine (hospitalization, ICU admission, or Mechanical ventilation)

- Evaluate the safety of investigational drug compared to the control arm within 15 days after starting the medicine. This is assessed by allergic reactions, medication intolerance, liver toxicity, and hyperuricemia in subjects.

PARTICIPANT DISCONTINUATION

Premature discontinuation of the trial would be based on the decision of the Data Safety Monitoring Board (DSMB), or the investigator-initiated based on the following:

1. Adverse event: clinical or laboratory event, that in the medical judgment of the investigator, for the best interest of the patient are grounds for discontinuation
2. A major deviation from the protocol: the patient's findings or conduct failed to adhere to the protocol requirements.

Other reasons: e.g., an administrative problem such as termination of study by the sponsor.

DATA COLLECTION, MANAGEMENT AND ANALYSIS

The research coordinator with expertise in data entry will enter data into a password-protected database (REDCAP). All observations and other data pertinent to the clinical investigation will be recorded into the e-CRF. Data will be entered and double-checked for accuracy. After resolving any discrepancies and a combination of manual and automated data-review procedures, the final data set will be subject to a quality assurance audit.

A clinical data management review will be performed on all subject data to ensure clinical data quality across all participants and sites. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. Also, the data will be reviewed for adherence to the protocol. During data analysis, non-identifiable data will be provided in a password protected excel sheet. All data are de-identified and coded with a unique number generated by the online data management system REDCAP.

SAFETY AND ADVERSE EVENTS MONITORING

All adverse events (AE) and serious adverse event (SAE) encountered during the clinical study will be reported on the e-CRF. The information to be entered in the e-CRF will include:

- The time of onset of any AE or the worsening of a previously observed AE
- The specific type of reaction in standard medical terminology

- The duration of the AE (start and stop dates)
- The severity of the adverse event (AE). The severity should be rated as:
    - Mild: discomfort noted, but no disruption of normal daily activity.
    - Moderate: discomfort noted of sufficient severity to reduce or adversely affect normal activity.
    - Severe: incapacitating, with the inability to work or perform normal daily activity.
- The assessment of the relationship of adverse event (AE) to study medication, i.e., according to the definitions below:
    - Related: with a reasonable causal relationship to the investigational product.
    - Not Related: without a reasonable causal relationship to the investigational product.
    - Other: in such a case, the investigator's causality assessment should be specified.
- Description of action taken in treating the AE and/or change in study medication administration or dose.

As far as possible, all investigators will follow-up participants with AEs until the event is resolved or until, in the investigator's opinion, the event is stabilized or determined to be chronic. Details of AE resolution will be documented in the e-CRF. Any significant changes in AEs will be reported even though the subject has completed the study, including the protocol-required post-treatment follow-up.

STATISTICAL METHODS

General Considerations

This is a randomized, double-blinded study comparing Favipiravir tablets to placebo group to treat subjects with mild SARS-CoV-2 infection. The Intention to treat (ITT) analysis will include all subjects randomized which will ignore noncompliance, protocol deviations, withdrawal, and anything that will take place after randomization. (17, 18) The primary analysis population for evaluating both efficacy and safety outcomes will be a modified ITT population, and will include all subjects who have been randomized but will exclude some randomized subjects like patients who were judged ineligible after randomization or patients who withdrew consent or certain

patients who never started treatment (17, 18), study drug (Favipiravir tablets or Placebo) was started, and the patient did not withdraw consent. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

Sample Size and Power Considerations

Assumptions and Study Hypothesis

a. The current study's primary hypothesis is H0: HR =1 vs. H1: HR ≠1; and HR is the hazard ratio of treatment compared to control arm.

b. Time to viral clearance

In patients with mild COVID-19, 90% of the patients clear the virus by day 10 of onset.(1) If we assume an exponential hazard, we estimate the median time of viral clearance in the placebo group to be 8 days.

c. The exact treatment effect from Favipiravir is not known but can be approximated using prior clinical studies. A study comparing Favipiravir's effect to lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral clearance in the Favipiravir arm.(19) To stay on the conservative side, we assume that Favipiravir will reduce the median time to virus clearance to 6 days which is equivalent to hazard ratio of 1.33.

d. We further assume that 90% of the control group patients will have viral clearance within 15 days, and 90% will have viral clearance in the treatment arm. It is anticipated that very few of these subjects will be randomized and not start study treatment (and so be excluded from the primary analysis) or be lost to follow-up (and so have missing data for the primary endpoint). Given certain uncertainties however, we have included a nominal 10% drop out rate.

Sample Size Estimation for Classical Two Arm Parallel Design

Under the classical two-arm parallel design, a one-sided test of whether the hazard ratio is 1 with an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is 1.330.

The sample size re-estimation will be based on the ratio of the planned effect size (1.33) to the observed effect size from the interim analysis according to the following formula:

$$N = \left(\frac{E_0}{E}\right)^a N_0$$

where 'a' is a constant which will be set to 2 and is a number chosen to be slightly larger than the classical sample size per group, is the planned effect size of 1.33, and E is the observed effect size from the interim analysis.

A detailed statistical analysis plan will be developed before undertaking any comparative analyses of outcomes. The following provides a summary of the approach to analysis for the primary endpoint**.**

Analysis of the primary endpoint:

The primary endpoint of the current study is the rate of viral clearance. The number and percent of subjects who met the endpoint by day 15 of follow up will be calculated and tabulated. Due to the nature of the data collection (i.e., subjects clearance will be observed during specific follow-up time), survival analysis methods for interval-censored data will be used to analyze the data. All results will be reported in H.R and the corresponding lower confidence limit and one-sided p-value.

Analysis for secondary endpoints:

- Quantitative variables such as 'change from baseline in clinical scores' are expected to have reasonably skewed distributions. They may be subject to censoring, e.g., for subjects in hospital on day 28, compared between randomized arms using non-parametric tests (Wilcoxon's test).
- Analysis of the other secondary endpoints will use a proportional odds model with an indicator variable for randomized treatment. The Wald test will generate a p-value comparing treatments and the estimated proportional odds ratio comparing treatments with associated 95% CI.
- Analysis of AE data will primarily be descriptive based on MedDRA coding of events. The proportion of subjects experiencing an SAE and the proportion experiencing a Grade

- Three or higher AEs will be compared between randomized arms using Fisher's Exact Test.

For enrolled subjects who were not randomized (i.e., screen failures) or randomized but did not receive the treatment, the final analysis will detail safety (deaths and SAEs) and reasons they were not randomized or did not receive treatment, respectively.

DATA MONITORING:

This committee will be independent of the sponsor with relevant therapeutic and biostatistical experience to allow for the ongoing review of data from this trial. A Data and Safety Management Board (DSMB) will be convened to monitor the trial's unblinded data focusing mainly on assuring that the study follows the protocol correctly and monitoring the safety issues related to the trial. The DSMB will meet when AEs trigger study pausing/stopping criteria are triggered. The DSMB has no competing interests.

The current study will have a single interim analysis, which will occur after the recruitment and follow-up of 40% of the total number of subjects (i.e., 230 subjects). The interim analysis is designed to test for early stopping for futility or efficacy and sample size re-estimation.(20) The interim analysis and final analysis will be based on the sum of the stage-wise p-value. Table 2 describes the interim analysis testing boundaries.

Table 2: Interim analysis and sample size Re-estimation

Alpha1 = 0.01	Stop the trial for early efficacy if the interim analysis p-value is less than 0.01
Beta1 =0.25	Stop the trial for futility if the interim analysis P-value is equal to or larger than 0.25
Alpha2=0.1832	Declare the trial significant if the sum of the interim analysis and final stage P-values are less than 0.1832

Frequency and procedures for auditing trial conduct:

The investigator will allow representatives of the regulatory authorities (Saudi Food & Drugs Authority) to conduct an audit anytime they request it. The regulatory authorities are independent from the sponsor.

DISCUSSION

During the Ebola virus disease outbreak, the JIKI trial illustrated an improved survival rate in patients with moderate to high viral load with favipiravir. (21) Similarly, Bai et al.'s study proved a significant decline in viral load with favipiravir in patients with moderate viral load at baseline. (22) These findings support the role of favipiravir in viral load reduction. Since the homology of gene sequences of SARS-CoV-2 and SARS was over 90%, it is expected that the intervention of antiviral drugs in COVID-19 patients will likely improve or shorten the time to viral clearance. (23) The reduction in time to viral clearance is chosen as the endpoint based on the above evidence. Therefore, viral clearance, which captures the viral shedding duration and possible contagiousness period, reflects the best assessment. Several published trials have studied similar endpoints as our study due to their clinical significance. A study of 80 patients with COVID-19 compared Favipiravir to lopinavir/ritonavir. The study reported a shorter viral clearance time for the Favipiravir arm versus the lopinavir/ritonavir arm median 4 days (IQR: 2.5–9) versus 11days (IQR: 8–13), $P < 0.001$). Multivariable Cox regression showed that favipiravir was significantly ($p = 0.026$) associated with faster viral clearance. Additionally the timing of antiviral therapy reached near significance ($p = 0.055$). (19) Furthermore, it was superior to Arbidol in having a higher 7-day clinical recovery rate in patients with COVID-19 and a more significant reduction in fever and cough (15). A Japanese observational study assessed the safety and efficacy of favipiravir. The median duration of therapy was 11 days, with reported clinical improvement rates at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and 60.3% for mild, moderate, and severe disease, respectively. (24) A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19 chose the primary endpoint was viral clearance by day 6. The secondary endpoint was a change in viral load by day 6. Additionally, exploratory endpoints included time to defervescence and resolution of symptoms. (25) A trial from Russia enrolled 60 patients (40 on favipiravir and 20 on Supportive Care) with primary endpoint as viral elimination. The secondary endpoints were defervescence and RT-PCR negativity. (13) Lately, a phase 3, open-

label, randomized, multicenter study (Glenmark Pharmaceuticals) was initiated in India. The primary endpoint was time until the cessation of oral shedding of the SARS-CoV-2 virus. (26)

According to a study by Jones et al., there are 630 registered trials for COVID-19 on the clinicaltrials.gov website by 1 May, 2020. Most of these trials are from Europe, the USA, China, and other Asian countries. Additionally, all the trials on the drugs or biologics (218) are studying drugs like hydroxychloroquine or chloroquine (88), azithromycin (53), and 25 trials assessing convalescent plasma, lopinavir/ ritonavir, stem cell treatments, and tocilizumab. (27)

Another study reported 201 trials registered with the US registry and WHO clinical trials registry platform. Out of these, 93.5% studied drug intervention. From the total trials, 49.8% were from China, 37.8% USA accounting for 87.6% of both countries studies. From the 201 trials, only 11 trials are being done on Favipiravir. (28) As of 23 July 2020, there are 32 studies registered on clinicaltrials.gov to assess this drug's utility in the management of COVID-19 (3 completed, 12 recruiting). (29)

Many clinical trials conducted in China, Japan, Russia, and India had an open-label design, which leads to reporting biased results. (13, 19, 25, 26) Recently a study was done in India on Favipiravir in mild to moderate COVID-19 Cases. This was a randomized, open-label study and the sample size of only 150 patients. (30) There are certain limitations reported in this study, which were due to the small sample size. The hazard ratio reported was small, and due to the study's open-label nature, it may have been subjected to potential bias. This study's primary endpoint was confounded due to interpretation issues with RT-PCR positivity and its lack of correlation with the clinical cure. (30)

A systemic review and meta-analysis of Favipiravir reported evidence showing potential benefits of this drug in clinical and imaging improvement after treating COVID-19 patients. Therefore there is a need for additional randomized, double-blind clinical trials to form a definite opinion about the rationale to use this drug. There were several drawbacks to the studies that have already been published, such as non-randomized design, small sample sizes, and different durations of treatment, different dosage regimes, and lack of blinding. (31)

In our study, we adopted the design double-blind, placebo-controlled randomized study, which provides the best evidence of causation. (32) Randomized double-blind placebo control studies

(RDPCS) are regarded as the "gold standard" of epidemiologic studies. They are employed to illustrate superiority, equivalence, and non-inferiority. Well-designed RDPCS gives the most robust possible evidence of causation. The benefits of randomization are 1. It avoids selection bias that may happen if either the physician or the patient decides the treatment, 2. It removes most confounding by all known and unknown factors as it prevents an association between the treatment and any other known or unknown factor. Blinding with randomization evades reporting bias as no one is aware of the treatment; hence all treatment groups will be treated the same. The use of placebo as control leads to the placebo effect where the person on placebo will think that they are taking the actual treatment, which leads them to feel better or respond to it due to wishful thinking. The presence of placebo control will help to compare the drug's effectiveness against the placebo's effectiveness (33-35)

There are currently only two countries (KSA and Kuwait) from the Middle East with ongoing Favipiravir trials with a placebo comparator. (29) Our study is the first trial registered from the Middle East region to date funded by the government of KSA. Our study's sample size is 576 subjects, the second largest to Kuwait's trial (780) from the presently ongoing Favipiravir trials.(29)

LIMITATIONS

Numerous challenges are expected during this trial. The trial is ongoing now during restricted travel time, and hospitals restricted nonessential personnel's entry. Protocol training, site initiation visits, and monitoring visits will be performed remotely in many sites. The research team will be assigned to other clinical services, and many members require extra effort. Also, study team member's sicknesses or unprotected exposure to COVID-19 patient strained research resources. Many sites may encounter inadequate supplies of personal protective equipment and trial-related supplies. The study is prone to certain biases due to the design, such as non-compliance, withdrawals after randomization, and attrition/losses to follow-up.

ETHICS AND DISSEMINATION

This study will be carried out in compliance with the protocol and by the laws and regulations of King Abdullah International Medical Research Centre Ethics Committee (KAIMRC IRB) and the Ministry of Health Ethics Committee (MOH IRB). The date for approval for the first version was 28 April 2020, and for the protocol version, V2.2 is 25 November 2020. KAIMRC IRB

approved this study with protocol number RC20/220. The study applies the principles established in the Declaration of Helsinki. The participants will sign a written informed consent form (ICF-supplementary material 2) before the first assessment and data collection by delegated personnel. Contact details of the principal investigator are provided to the patients for queries and concerns. Patients are free to withdraw from the study at any time without any consequences regarding their standard clinical care. Any change or addition to this protocol requires a written amendment approved by the sponsor and the investigators. Before implementation, the investigators will transmit all major amendments to the Ethics Committees, examining the initial protocol. The investigators will transmit a copy of the Ethics Committee's opinion to the sponsor. The investigators will notify all minor amendments to the Ethics Committee that had examined the initial protocol. All amendments will be reported to the clinical trials registration site.

TRIAL STATUS

This trial began on 23 July 2020. On 3 March 2021, 191 patients have been enrolled.

DATA SHARING PLAN

Study protocol and statistical plan will be openly available.

PATIENT AND PUBLIC INVOLVEMENT

This research was done without patient and public involvement due to time constraints. The results of the study will be disseminated to the public via social media platforms.

ACKNOWLEDGEMENTS

We acknowledge principal investigators for all sites (alphabetical order): Ali Tolba, Hanan Turkistany, Mohannad Bahlaq, Saad Alshahrani, Sanaa Al Rehily, Zied Ghaifer Ali. We thank all staff involved in data monitoring.

Figure 1 Overview of Study

Figure 2 Schedule of Enrollment

REFERENCES

1. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. The Lancet Infectious Diseases. 2020;20(6):656-7.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
3. Worldometers.info. Totoal Coronavirus Cases in Saudi Arabia [internet]. Dover, Delaware, U.S.A.: Worldometer; 2021 [updated 25 Feb 2021; cited 2021 25 Feb]. Available from: https://www.worldometers.info/coronavirus/country/saudi-arabia/.
4. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacology & therapeutics. 2020;209:107512.
5. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews Drug discovery. 2020;19(3):149-50.
6. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral research. 2018;153:85-94.
7. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy Series B, Physical and biological sciences. 2017;93(7):449-63.
8. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) [Internet]. online: Centre For Disease Control and Prevention; 2020 [updated Dec 8,2020; cited 2021 18 Jan]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
9. COVID-19. Coronavirus Disease Guidelines [online]. Kingdom of Saudi Arabia: Ministry of Health; 2020 [cited 2021 18 Jan]. Available from: https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx.
10. Compendium of Guidelines,Instruction and Standard Operative Procedures for Covid-19 [Internet]. India: Medical Education and Drugs Department Government of Maharashtra; 2020 [cited 2021 18 Jan]. 4:[Available from: https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volume%204.pdf.
11. Ratanarat R, Sivakorn C, Viarasilpa T, Schultz MJ. Critical Care Management of Patients with COVID-19: Early Experience in Thailand. Am J Trop Med Hyg. 2020;103(1):48-54.
12. Interim guidelines. Prevention, diagnostics and treatment of a new coronavirus infection (COVID-19) [Internet]. Russia: MOH of the Russian Federation; 2020 [updated 28 April 2020; cited 2021 18 Jan]. 6:[Available from: https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf.
13. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases. 2021;102:501-8.
14. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Annals of Internal Medicine. 2013;158(3):200-7.

15. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020:2020.03.17.20037432.
16. Favipiravir: Report on the Deliberation Results;. 2014. Japan: Toyama Chemical, Evaluation and Licensing Division PaFSBMoH, Labour and Welfare; 2014 March 4 Report No.
17. Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. The Medical journal of Australia. 2003;179(8):438-40.
18. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res. 2011;2(3):109-12.
19. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing, China). 2020.
20. Kumar A, Chakraborty BS. Interim analysis: A rational approach of decision making in clinical trial. J Adv Pharm Technol Res. 2016;7(4):118-22.
21. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. PLoS medicine. 2016;13(3):e1001967.
22. Bai CQ, Mu JS, Kargbo D, Song YB, Niu WK, Nie WM, et al. Clinical and Virological Characteristics of Ebola Virus Disease Patients Treated With Favipiravir (T-705)-Sierra Leone, 2014. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(10):1288-94.
23. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727-33.
24. James MI. Preliminary report of favipiravir observational study in Japan released. online: News-Medical.net, 2020.
25. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19. Antimicrobial Agents and Chemotherapy. 2020;64(12):e01897-20.
26. Singh P. A Clinical Study on Favipiravir Compared to Standard Supportive Care in Patients With Mild to Moderate COVID-19 [Online]. Cochrane COVID-19 Study Register2020 [updated April]. Version 3 [Available from: ICTRP (http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43504).
27. Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered with ClinicalTrials.gov: cross-sectional analysis. BMJ Open. 2020;10(9):e041276.
28. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical trials assessing treatments for COVID-19: a cross-sectional analysis. BMJ Open. 2020;10(6):e039978.
29. Listed COVID 19 Studies [Internet]. online: US National Institue of Health (NIH); 2020 [cited 2020 26 Nov]. Clinicaltrials.org]. Available from: https://www.clinicaltrials.gov.
30. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and Safety of Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial. International Journal of Infectious Diseases. 2020.
31. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. Virology journal. 2020;17(1):141.
32. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ. 2000;321(7256):255-6.
33. Oleckno WA. Essential Epidemiology: Principles and Applications. 4180 IL route 83, suite 101 Long Groove, IL: Waveland Press, Inc.; 2002.
34. Hulley S, Cummings S, Browner W, Grady D, Newman T. Designing clinical research. 503 Walnut street, Philadelphia, PA, USA: Williams and Wilkins .A Walters Kluwer business Lippincot; 2007.
35. Manja V, Lakshminrusimha S. Epidemiology and Clinical Research Design, Part 1: Study Types. Neoreviews. 2014;15(12):e558-e69.

AUTHOR CONTRIBUTIONS

MoB, AhH, MoA, KhS, AbM, HaQ, MaS, EbM, AdA, AbA, SaA, MaJ, and AhA participated in study design and protocol development. MoB, AbM, KhA, KhS, AbA are involved in subject recruitment and follow-up plan. MoH, OmA, AhA, and MoB participated in the development of statistical analysis plan. KhS, MoB, AbA, and AhH contributed to manuscript preparation. KhS and MoB contributed to review and manuscript submission.

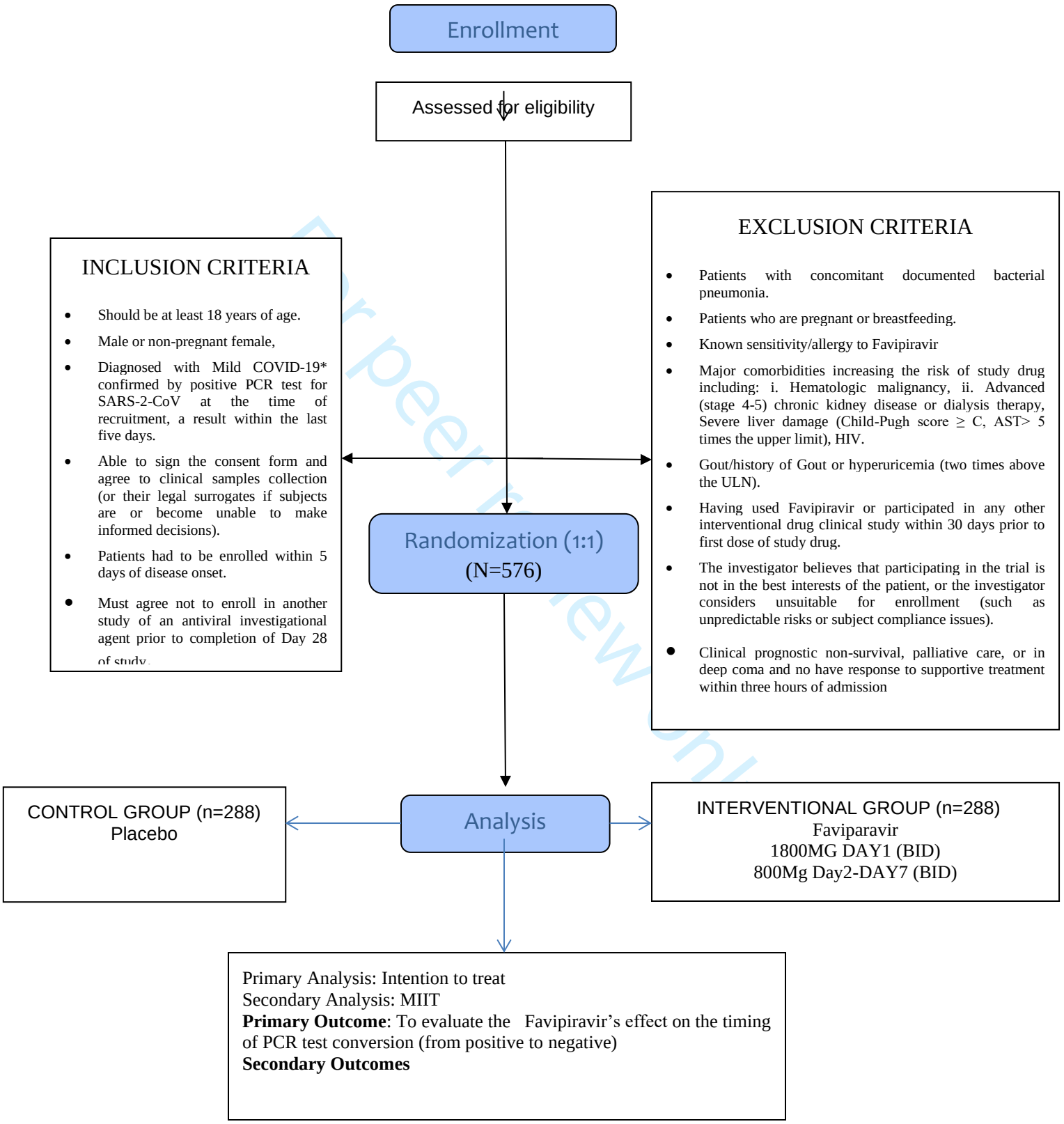
FUNDING

This trial was funded by King Abdullah International Research Centre, KSA (grant no. RC20/220/R).

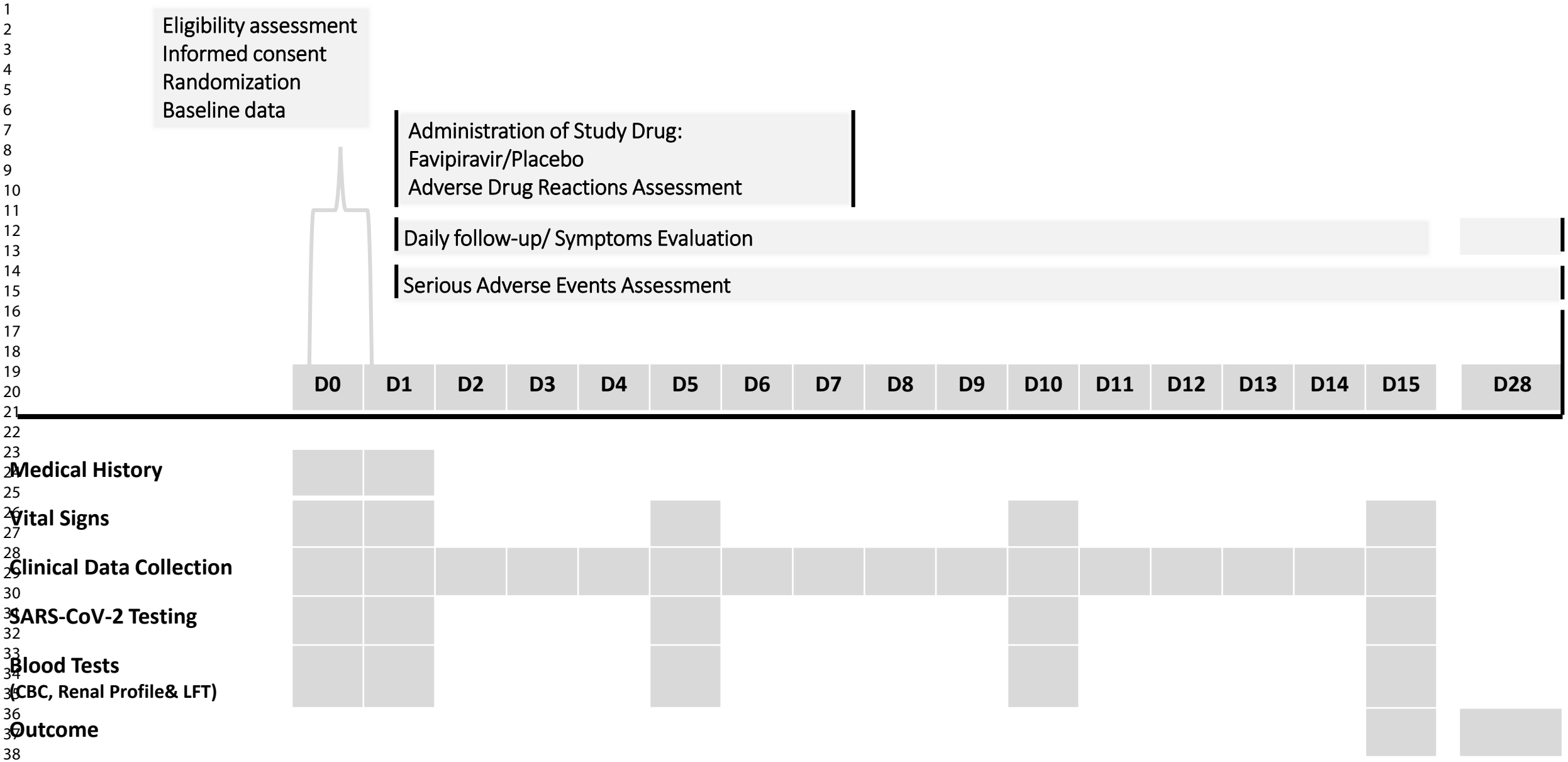
COMPETING INTERESTS

Authors declare no competing interest.

Fig1: AviMild arms. BID, two times per day; MIIT, modified intention to treat



Enrollment Process in Avi-Mild19 Clinical Trial



Demographics And Epidemiological Factors

Record ID	_____
Demographics	
Subject ID	_____
Patient Initial	_____
Date of Birth	_____
Age	_____ (year)
Enrolment date	_____
Ethnic group	◯ Arab ◯ Non Arab
Nationality	_____
Gender	◯ Male ◯ Female
Epidemiological Factors	
1.Close contact* with a confirmed or probable case of COVID-19 infection, while that patient was symptomatic	◯ Yes ◯ No ◯ Unknown
2.Presence in a healthcare facility where COVID-19 infections have been managed	◯ Yes ◯ No ◯ Unknown
3.Presence in a laboratory handling suspected or confirmed COVID-19 samples	◯ Yes ◯ No ◯ Unknown

Clinical Inclusion And Exclusion Criteria

Inclusion Criteria	
1.Male or non-pregnant female	◯ Yes ◯ No
2.Diagnosed with Mild COVID-19 by Positive PCR confirmed SARS-coV-2 all the time of recruitment	◯ Yes ◯ No
3.Able to sign the consent form and agree to clinical samples collection (or their legal surrogates if subjects are or become unable to make informed decisions).	◯ Yes ◯ No
4.Patient enrolled within 5 days of disease onset	◯ Yes ◯ No
5.Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study.	◯ Yes ◯ No
Exclusion Criteria	
1.Patients with concomitant documented bacterial pneumonia	◯ Yes ◯ No
2. Patients who are pregnant or breastfeeding	◯ Yes ◯ No
3. Known sensitivity/allergy to Favipiravir	◯ Yes ◯ No
4. Major comorbidities increasing the risk of study drug including: i. Hematologic malignancy, ii. Advanced (stage 4-5) chronic kidney disease or dialysis therapy, Severe liver damage (Child-Pugh score ≥ C, AST> 5 times the upper limit), HIV.	◯ Yes ◯ No
5. Gout/history of Gout or hyperuricemia (two times above the ULN)	◯ Yes ◯ No
6.Having used Favipiravir or participated in any other interventional drug clinical study within 30 days prior to first dose of study drug.	◯ Yes ◯ No

7.The investigator believes that participating in the trial is not in the best interests of the patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues)	◯ Yes ◯ No
8.Clinical prognostic non-survival, palliative care, or in deep coma and have no response to supportive treatment within three hours of admission	◯ Yes ◯ No
Randomization	
Site	◯ Site1 ◯ Site2 ◯ Site3 ◯ Site4 ◯ Site5 ◯ Site6 ◯ Site7 ◯ Site8 ◯ Site9 ◯ Site10
Patient Recruited in ?	◯ Hospital ◯ Community
Treatment	◯ A ◯ B ◯ C ◯ D
Randomization Time	_____

Co-Morbidities

Height

_____ (cm)

Weight

_____ (kg)

Co-morbidities and risk factors - Charlson Index will be calculated for each patient at analysis.

	Yes	No	NA
Hypertension	○	○	○
Chronic cardiac disease, including congenital heart disease (not hypertension)	○	○	○
Chronic pulmonary disease (not asthma)	○	○	○
Asthma (physician diagnosed)	○	○	○
Chronic kidney disease	○	○	○
Chronic liver disease	○	○	○
Chronic neurological disorder	○	○	○
Chronic Rheumatologic/Auto-immune disorder	○	○	○
Obesity (BMI more than 30)	○	○	○
Diabetes with complications	○	○	○
Diabetes without complications	○	○	○
Smoking	○	○	○
Other	○	○	○

Specify, Other Co-Morbidities

_____

Onset And Admission

At Other Facility

Onset date of first/earliest symptom	_____
Did the patient visit another health care facility since the onset date of first/earliest symptom?	◯ Yes ◯ No ◯ NA
Date of the visit	_____
Name of Facility	_____
City	_____
What health care was provided?	◯ Inpatient (Ward, ICU) ◯ Outpatient (ER, Clinic, Primary Care) ◯ NA ◯ Others
Was admission required?	◯ Yes ◯ No ◯ NA
Date of Admission	_____
Date of Discharge	_____

At This Facility

Location of Patient at the Time of Randomization	◯ Outpatient ◯ ER ◯ Ward
Was Admission Required?	◯ Yes ◯ No ◯ NA
Admission Date at this Facility	_____

Vital Signs At Randomization

(First Available Data at Presentation/Admission-within 24 Hours)	
Temperature	_____ (°C)
Heart Rate	_____ (Beats Per Minute)
Respiratory Rate	_____ (Breaths Per Minute)
Systolic BP	_____ (mmHg)
Diastolic BP	_____ (mmHg)
Oxygen Saturation:	_____ (%)
Oxygen saturation On:	◯ Room air ◯ Oxygen therapy ◯ NA
Specify Therapy	◯ Nasal Cannula ◯ Facemask ◯ Non- rebreathable mask ◯ High flow nasal cannula ◯ Non-invasive ventilation (BiPap, CPap) ◯ Invasive Mechanical Ventilation
Please, mention amount	_____
	◯ L/min ◯ %

Symptoms

Observed/reported at admission and associated with this episode of acute illness			
	Yes	No	NA
Fever	○	○	○
Cough	○	○	○
Cough with Sputum Production	○	○	○
Cough with Bloody Sputum/Haemoptysis	○	○	○
Sore Throat	○	○	○
Runny Nose (Rhinorrhoea)	○	○	○
Chest Pain	○	○	○
Shortness of Breath (Dyspnea)	○	○	○
Loss of smell	○	○	○
Loss of taste	○	○	○
Abdominal Pain	○	○	○
Vomiting / Nausea	○	○	○
Diarrhoea	○	○	○
Ear Pain	○	○	○
Muscle Aches (Myalgia)	○	○	○
Joint Pain (Arthralgia)	○	○	○
Fatigue / Malaise	○	○	○
Lower Chest Wall Indrawing	○	○	○
Headache	○	○	○
Conjunctivitis	○	○	○
Skin Rash	○	○	○
Skin Ulcers	○	○	○
Lymphadenopathy	○	○	○

Daily Clinical Assesment

Complete one form on admission, one form on admission to ICU, and daily up to 28 days or until discharge or death if earlier. Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A')

Study Day (clinical assesment study day start on 2nd day after randomization)	_____ (Day)
Date of Phone Assesment	_____
Time	_____
Current admission to ICU?	◯ Yes ◯ No
FiO2 (0.21-1.0)	_____
SaO2	_____ (%)
PaO2 at time of FiO2 above	_____
	◯ kPa ◯ mmHg
PaO2 sample type:	◯ Arterial ◯ Venous ◯ Capillary ◯ N/A
From same blood gas record as PaO2	_____
	◯ kPa ◯ mmHg
pH	_____
HCO3	_____ (mEq/L)

Systolic Blood Pressure	_____ (mmHg)
Diastolic Blood Pressure	_____ (mmHg)
Mean Arterial Blood Pressure	_____ (mmHg)
Urine flow rate	_____ (mL/24 hoursCheck if estimated)
Glasgow Coma Score (GCS / 15)	_____

Is the patient currently receiving, or has received (between 00:00 to 24:00 on day of assessment) (apply to all questions in this section):

	Yes	No	N/A
Non-invasive ventilation (e.g. BIPAP, CPAP)	◯	◯	◯
Invasive ventilation	◯	◯	◯
Extra corporeal life support (ECLS)	◯	◯	◯
High-flow nasal cannula oxygen therapy	◯	◯	◯
Dialysis/Hemofiltration	◯	◯	◯
Any vasopressor/inotropic support	◯	◯	◯

Progress of Symptoms at 1st Presentation(pyrexia, short of breath, and relief of cough and/or others) Can stop recording if resolved for 72 hours

◯ Worsening
◯ Same
◯ Better
◯ Resolved

Signs and Symptoms

New signs and symptoms	◯ Yes ◯ No
Specify,	_____ (L/min)
Starting Date	_____
Fever	◯ Yes, ◯ No

Fever Result	_____ (°C)
Any hospital/ER visits	◯ Yes ◯ No
Was Vital Signs Collected?	◯ Yes ◯ No
Temperature	_____ (°C)
Heart Rate	_____ (Beat Per Minut)
Respiratory Rate	_____ (Breath Per Minute)
Systolic Blood Pressure	_____ (mmHg)
Diastolic Blood Pressure	_____ (mmHg)
Oxygen Saturation	_____ (%)
Oxygen On	◯ Room air ◯ Oxygen therapy ◯ NA
Specify, Oxygen Therapy	_____

SARS-2-COV Testing

Sample study day	◯ Day 1(-5 day) ◯ Day 5 (+/- 1 day) ◯ Day 10 (+/-1 day) ◯ Day 15 (+/- 2 day)
Collection Date	_____
Biospecimen Type	◯ Nasopharyngeal swab ◯ Oropharyngeal swab ◯ Combined Nasopharyngeal and Oropharyngeal swab ◯ Sputum ◯ BAL
Laboratory labResult	◯ Positive ◯ Negative ◯ NA

Lab Assessment Form

Complete one form on admission, one form on admission to ICU, and daily up to 28 days or until discharge or death if earlier. Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A')

Study Day

- ◯ Day 1 (+1 day)
- ◯ Day 5 (±1 day)
- ◯ Day 10 (±1 day)
- ◯ Day 15 (±2 day)

Laboratory Assessement

Haemoglobin

_____

◯ g/L ◯ g/dL

WBC Count

_____

◯ x109/L ◯ x103/µL

Lymphocyte count

_____
(cells/ µL)

Neutrophil count

_____
(cells/ µL)

Platelets

_____

◯ x109/L ◯ x103/µL

ALT/SGPT

_____
(U/L)

Total Bilirubin

_____

◯ µmol/L ◯ mg/dL

AST/SGOT

_____
(U/L)

Glucose

_____

	◯ mmol/L ◯ mg/dL
Blood Urea Nitrogen (urea)	_____
	◯ mmol/L ◯ mg/dL
	◯ mmol/L ◯ mg/dL
Creatinine	_____
	◯ umol/L ◯ mg/dL
Sodium	_____ (mEq/L)
Potassium	_____ (mEq/L)
Chest X-Ray performed?	◯ Yes ◯ No ◯ NA
Were Infiltrates Present?	◯ Yes-Unilateral ◯ Yes - Bilateral ◯ No ◯ NA
.	
ECG performed?	◯ Yes ◯ No ◯ N/A
if YES QT Interval	_____

Daily Study Drug

Favipiravir / Placebo	
Was Favipiravir given?	◯ Yes ◯ No
Dose	_____
Dose Number	_____
Date	_____
Time given	_____
Drug Method	◯ Syrup ◯ tablet

Pathogen Testing

Was Other pathogen testing done during this illness episode?	◯ Yes ◯ No ◯ NA
Bacteria	◯ Yes - confirmed ◯ No
What Bacteria?	_____
Other Infectious Respiratory Diagnosis	◯ Yes- Confirmed ◯ Yes- Probable ◯ No
Specify, Other Infectious Respiratory Diagnosis	_____
If None of the Above , Suspected Non-Infective	◯ Yes ◯ No

Complication (At day 28)

At any time during hospitalization did the patient experience:	Yes	No
Pulmonary Embolism	○	○
Bacterial Pneumonia	○	○
Coagulopathy	○	○
Acute lung Injury/ARDS	○	○
Anemia	○	○
Pneumothorax	○	○
Pleural Effusion	○	○
Acute renal Injury/Failure	○	○
Seizure	○	○
Congestive Heart Failure	○	○
Meningitis/ Encephalitis	○	○
Stroke/Cerebrovascular Accident	○	○
Endocarditis / Myocarditis / Pericarditis	○	○
Cardiac Arrhythmia	○	○
Bacteremia	○	○
Cardiac Arrest	○	○
Liver Dysfunction	○	○
Rhabdomyolysis / Myositis	○	○
Other	○	○

Specify other Complication _____

Treatment

At any time during enrollment did the patient receive/undergo?	
Hospital admission?	◯ YES ◯ NO ◯ N/A
date of hospital admission	_____
date of hospital discharge	_____
ICU or High Dependency Unit Admission?	◯ Yes ◯ No ◯ NA
Date of ICU Admission	_____
Date of ICU Discharge	_____
Oxygen Therapy?	◯ Yes ◯ No ◯ NA
Specify therapy	_____
Non-invasive Ventilation? (e.g. BIPAP, CPAP)	◯ Yes ◯ No ◯ NA
Invasive Ventilation (Any)?	◯ Yes ◯ No ◯ NA
Total Duration	_____ (Days)
Tracheostomy Inserted	◯ Yes ◯ No ◯ NA
ECMO?	◯ Yes ◯ No ◯ NA
Renal Replacement Therapy (RRT) or Dialysis?	◯ Yes ◯ No ◯ NA
Inotropes/Vasopressors?	◯ Yes ◯ No ◯ NA
First/Start Date	_____

Last/End Date	
OTHER Intervention or Procedure	

Medication

Antiviral Agent?	◯ Yes ◯ No ◯ NA
Specify, Antiviral Agent	☐ Favipiravir ☐ Hydroxychloroquine ☐ chloroquine ☐ Lopinavir/Ritonavir ☐ Azithromycin ☐ Interferon ☐ Oseltamivir
Favipiravir Dose	_____
Favipiravir_ start date	_____
Favipiravir_ end date	_____
Hydroxychloroquine Dose	_____
Hydroxychloroquine_Start date	_____
Hydroxychloroquine_End date	_____
Chloroquine Dose	_____
Chloroquine _Start date	_____
Chloroquine _End date	_____
Lopinavir/Ritonavir Dose	_____
Lopinavir/Ritonavir_Start Date	_____
Lopinavir/Ritonavir_End Date	_____
Azithromycin Dose	_____
Azithromycin_Start date	_____

Azithromycin_end date	_____
Interferon Dose	_____
Interferon_Start date	_____
Interferon_End date	_____
Oseltamivir Dose	_____
Oseltamivir_Start date	_____
Oseltamivir_End date	_____
Anti-Interleukin-6 Agents?	◯ Yes ◯ No
Please ,Provide Type	_____
Please ,Provide the Dose	_____
Antibiotic?	◯ Yes ◯ No ◯ NA
Dose	_____
Type	_____
Is the patient take another antibiotic?	◯ Yes ◯ No ◯ NA
Antibiotic_2 Type	_____
Antibiotic_2 Dose	_____
Antibiotic_3 Type	_____
Antibiotic_3 Dose	_____

Antibiotic_4 Type	_____
Antibiotic_4 Dose	_____
Convalescent plasma?	◯ Yes ◯ No ◯ N/A
Specify	_____
Corticosteriod?	◯ Yes ◯ No
Dose	_____
Type	_____
Duration	_____

Outcome

Outcome at Day 14	
Outcome at day 14:	☐ Alive ☐ Hospitalization ☐ Transfer to other facility ☐ Death ☐ Unknown
Outcome Date	_____
Hospital Discharge Date	_____
Outcome at Day 28	
Outcome at Day 28	◯ Alive ◯ Death
Outcome Date	_____

Adverse Drug Reaction

Allergic Reaction	
Day	_____
Skin Rash/Urticaria	◯ No ◯ 1 ◯ 2 ◯ 3
Bronchospasm	◯ No ◯ 1 ◯ 2 ◯ 3
Dyspnea	◯ No ◯ 1 ◯ 2 ◯ 3
Tongue Edema	◯ No ◯ 1 ◯ 2 ◯ 3
Local Skin Necrosis at the Injection Site	◯ No ◯ 1 ◯ 2 ◯ 3
OtherI	◯ No ◯ 1 ◯ 2 ◯ 3
Specify,	_____
OtherII	◯ No ◯ 1 ◯ 2 ◯ 3
Specify,	_____
Gastrointestinal	
Diarrhea	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Dysgeusia	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Nausea	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Vomiting	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Abdominal Pain	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5

OtherI	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____
OtherII	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____

Central Nervous System

Headache	◯ No ◯ 1 ◯ 2 ◯ 3
Insomnia	◯ No ◯ 1 ◯ 2 ◯ 3
Psychosis	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Depression	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Mania	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
ECG: QT Interval Changes	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
OtherI	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____
OtherII	◯ No ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Specify,	_____

Kingdom of Saudi Arabia
Ministry of National Guard - Health Affairs

المملكة العربية السعودية
وزارة الحرس الوطني – الشؤون الصحية

Informed Consent for Research Study – Interventional Studies

Study Title	:	**A Trial of Favipiravir in Adults with Mild Coronavirus Disease Covid-19**
Study No.	:	
ICF version and date:		**V2, 15/09/2020**
Principal Investigator	:	**Dr. Mohammad Bosaeed**
Sponsor	:	**King Abdullah International Medical Research Center (KAIMRC)**
Principal Investigator Address	:	**King Abdulaziz Medical City- Riyadh Department of Medicine (MC 1443) P. O. Box 22490 Riyadh 11426 +966(0)18011111 Ext. 17535. bosaeedmo@ngha.med.sa**

1. Introduction:

- You are being invited to take part voluntarily in a research study because you have a mild COVID-19 infection. We are studying an antiviral medication called FAVIPARAVIR. This antiviral drug is approved in other countries like Japan to be used for influenza virus. We want to study its effect on the COVID-19 infection. Many countries like USA, Japan Italy and India are doing similar studies to see the effect of this antiviral medication in decreasing the illness caused due to COVID-19 infection.

- Please take time to read this information carefully. Discuss it with any one you want for the right advice (This may include a friend, a relative or a family doctor).

2. Study Purpose:

- This is a research study. The purpose of this study is to measure the effect of this medication on time of viral shedding and the resolution of symptoms like tiredness and lack of energy, fever, cough, and shortness of breath, sore throat, nasal congestion, vomiting, diarrhea etc. This study will also measure how safe this medication is to be used in treating COVID19 infection.

3. Duration of Participation:

- If you agree to participate in the trial, you will be required to take the medication for maximum period of 7 days. You will be followed up every day for 14 days to monitor your condition. We will also check on you on day 28 for a follow up on your well-being.

4. Number of Subjects participating/ study Area and settings:

- In this research study 576 patients like you will be participating. This study will be conducted in King Abdulaziz Medical City -Riyadh and other hospitals across the Kingdom.

5. Study Procedures:

- You will be put in a group randomly (like flipping a coin) to antiviral Favipiravir or the Placebo group (these are pills that look like Faviparavir but they have no effect on your body or your infection.)
- You will receive Favipiravir (AVIGAN) or placebo 1800mg i.e. 9 tablets on the 1st day two times in a day, then from next day till day 7 the dose will change to 800mg i.e. 4 tablets, two times by mouth.

- You will have a 50% chance of receiving either the medication Faviparavir or placebo.

Patient responsibility:

- You will need to record all the doses of the medication you will take at home in the given medication log
- If you miss a dose ,please record it as missed dose
- At the end of 7 days, please kindly bring back the empty bottle or the bottle with missed pills. Also bring the medication log you used to record the pills you took.
- You will need to come back to your study doctor on the day 5, 10 and 15 counting from the day you signed this consent and we will collect blood samples with a swab from your throat, nose or a sputum sample.

6. When will my participation end?

You will take this medication for a maximum of 7 days only. We will follow-up with you every day to check on your health for 14 days. We will check again on day 28 to know your well-being.

7. Risks and inconveniences:

- Like with all other medications this medication can also have some side effects that are common. These include increase in uric acid levels, diarrhea, abnormal liver tests and decrease in neutrophil count(neutrophils are type of white blood cells in your body that help to fight infection)
- Some people might have an allergic reaction to any of the ingredients of this medication.
- As you are required to give blood for lab tests on day 5, 10 and 15, the blood draw can cause bruising or pain at the site of blood draw. In some people this can cause fainting and rarely there can be infection at the site of blood draw
- Pregnant women will not be enrolled in this study. Male participants are advised to use the most effective contraceptive method during their participation and 7 days after the treatment ends. **Complication**: If pregnancy took place when you were taking this medication, information from animal studies showed that this medication spreads to sperm and cause the death of embryo or cause growing defects in embryos.
- There might be unknown reactions that can take place that we do not know yet.
- You will be informed with any new information that becomes available and this may affect your desire to start or continue the study.

8. Important information regarding females participation in the study:

If you are pregnant or suspect pregnancy, please inform us, as we cannot include pregnant or

suspected pregnant females in this study.

9. Costs and compensation for participation in this study:

You will not receive any compensation for your participation in this trial. However, in the event of an illness or injury related to the study medication, all treating procedures, follow-ups, hospitalization, will be provided to you immediately.

10. Benefits:

Previous studies done in USA and JAPAN have shown that this medication had a positive effect in treating influenza virus.

You may or may not benefit directly from participating in this research, but your participation may help other patients with COVID-19.

This research study will increase the medical knowledge which will help to decide if FAVAPIRAVIR medication can be used in treatment of COVID-19 in the future.

11. Alternative Treatment(s):

You will be receiving the routine treatment as per the treating physicians during the course of the study and you will be made aware of any new treatment available for the disease.

12. Information about participation:

Your participation in this study is totally voluntary, you have the right to withdraw at any time you want without mentioning the reasons. If you do not want to take part, you will receive standard care provided by your doctor, and your decision about the study will not affect your current or future medical care.

The study doctor and the study sponsor have the right to withdraw you from the study if he decided that it's better for your medical condition. Or you did not comply with study requirements.

If you have any other diseases or adverse events the principal investigator will decide whether to continue with participation in the study or not.

13. Confidentiality and Authorization to collect, use and disclose Personal Medical Information:

All information related to you including personal and medical data provided and collected by the study doctor and recorded in the study records will be handled as confidential and no one except authorized research team at King Abdullah International Medical Research Center (KAIMRC), Sponsors, Institutional Review Board (IRB), Research Scientific Committee (RC), Ministry of Health auditors, the Saudi Food and Drug Administration (SFDA) and related personnel that can have access to record, review and analyze them.

All the information collected in subjects records belong to King Abdullah International Medical Research Center. In case any results of the study are published, your personal information will never be mentioned, it may be coded in symbols known for research team

14. Communication

In case of any research related inquiries or medical care during study, or any injuries, emergency cases feel free to contact the study principal investigator **Dr. Mohammad Bosaeed** through Phone number: **+966(0)18011111 Ext. 17535.**
In case you have enquiries related to your rights as a research subject you can contact the Institutional Review Board on Tel. **0114294432** or **011429376**

- I've been given the opportunity to discuss my questions about participating in this study and the research team has answered all my questions, if I have any further questions I will call **Dr. Mohammad Bosaeed**

- I understand that my participation in this research is voluntary and I know that I have the right to withdraw when I decide without affecting the medical care that I receive usually and also understand that the principal investigator has the right end my participation as it deems appropriate to me.

- And I also understand that non-compliance with research procedures and/or the visits dates might end my participation of this study.

- I understand that every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

- By signing this informed consent form I acknowledged that I did not give up any of my legal rights, also I confirm that I have received a sufficient information about the study and that I have read and understood the information in this informed consent form and I have had the opportunity to discuss the study and ask questions and have been satisfied with the received explanations.

- I understand that after signing this informed consent form I will receive a signed and dated copy.
- By signing and dating this informed consent form, I agree to participate in this research study.

Subject Name	**Signature**	**Date**
Name of the legal guardian Type if the patient is minor (less than 18 years)	**Signature**	**Date**
Name of the witness Type if the subject agrees verbally and he/she is illiterate	**Signature**	**Date**
Name of the Principal Investigator	**Signature**	**Date**
Person who discussed the consent	**Signature**	**Date**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	3

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	3
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.