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# BMJ Open

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

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

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

**Word Count:** 2913

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3 **47 Abstract:**

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5 **48 Introduction**

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8 51 A novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of  
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10 52 respiratory illness termed Covid-19 in Dec 2019. There is lack of specific therapeutic agents  
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12 53 based on evidence for this novel coronavirus infections; however, several medications have been  
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14 54 evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease  
15  
16 55 the duration of virus carriage to limit the community's transmission.

17 **56 Methods and Analysis**

18  
19 58 We hypothesize that mild COVID19 patients treated with Favipiravir will have a shorter duration  
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21 59 of time to virus clearance than the control group. Primary outcome is to evaluate the effect of  
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23 60 Favipiravir on the timing of PCR test conversion from positive to negative within 15 days after  
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25 61 starting medicine.

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27 62 Adults (>18 years, Male or non-pregnant female, Diagnosed with Mild COVID-19 within five  
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29 63 days of disease onset) are being recruited by physicians participating from the Ministry of  
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31 64 National Guard Health Affairs and Ministry of Health ethics committee approved primary health  
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33 65 care centers. This double blind randomized trial comprises three significant parts screening,  
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35 66 treatment, and follow-up period, where treating physician and patients are blinded. Eligible  
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37 67 participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or a  
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39 68 control group (Placebo) with 1800 mg by mouth twice daily for first day, followed by 800mg  
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41 69 twice daily for 4-7 days. Serial nasopharyngeal/Oropharyngeal swab samples will be obtained on  
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43 70 day 1(-5 days before therapy). On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/  
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45 71 Oropharyngeal PCR COVID19 samples will be requested.

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47 72 The primary analysis population for evaluating both efficacy and safety outcomes will be a  
48  
49 73 modified ITT population. Anticipating a 10% drop-out rate, we expect to recruit 317 subjects per  
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51 74 arm. The results assume that the hazard ratio is constant throughout the study and that Cox  
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53 75 proportional hazards regression is used to analyze the data.

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## 81 **Ethics and dissemination**

82  
83 The study was approved by the King Abdullah Medical Research Centre Institutional Review  
84 Board and the Ministry of Health Institutional Review Board. Protocol details and any  
85 amendments will be reported to <https://clinicaltrials.gov/>. Results will be published in peer-  
86 reviewed journals.

87 **Trial registration number:** National Clinical Trial Registry (NCT04464408)

88  
89 **Funding:** This study was funded by King Abdullah International Medical Research Centre.

## 92 **Strengths and Limitations**

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

## 111 INTRODUCTION

112 In December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international  
113 outbreak of respiratory illness termed Covid-19. The WHO declared the epidemic of COVID-19  
114 as a pandemic on 12th March 2020. (1) According to a recent Chinese study, about 80% of  
115 patients present with mild disease, and the overall case-fatality rate is about 2.3% but reaches  
116 8.0% in patients aged 70 to 79 years. (2) Mild cases have been found to have viral loads 60-fold  
117 less than severe cases. The viral loads of asymptomatic individuals are lower, with possible  
118 implications for infectiousness and diagnosis(3) In Saudi Arabia, as of 27th March 2020, 1012  
119 confirmed cases of the disease were reported(4) There are no specific therapeutic agents based  
120 on substantial evidence for these novel coronavirus infections; however, several medications  
121 have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients  
122 and decrease the duration of virus carriage to limit the community's transmission.

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

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

### 134 Research hypothesis

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

## 137 METHODS

### 138 Study Design

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



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5 **143 Study Population**

6 144 A convenience sample of adult patients with mild COVID-19 infection identified as positive by  
7 145 PCR confirmed SARS-coV-2 who is eligible at the Ministry of National Guard Health Affairs at  
8 146 Riyadh and Madinah will be assessed for inclusion in the trial. Additionally positive patients  
9 147 visiting the Ministry of Health Institutional Review Board (IRB) and Saudi Food Drug Authority  
10 148 (SFDA) approved primary health care centers in the regions of Riyadh, Makkah and Madinah  
11 149 will also be assessed for eligibility. Figure 1 provides the CONSORT diagram for the trial  
12 150 procedure.

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20 **152 Inclusion Criteria and Exclusion Criteria**

21 153  
22 154 Inclusion criteria are: (1) Should be at least 18 years of age, (2) Male or non-pregnant female,  
23 155 (3) Diagnosed with Mild COVID-19\* confirmed by positive PCR test for SARS-2-CoV at the  
24 156 time of recruitment, a result within the last five days, (4) Patients have to be enrolled within 5  
25 157 days of disease onset. Exclusion criteria are (1) Patients with concomitant documented bacterial  
26 158 pneumonia (2) Patients who are pregnant or breastfeeding (3) Known sensitivity/allergy to  
27 159 Favipiravir, (4) Major comorbidities increasing the risk of study drug including: i. Hematologic  
28 160 malignancy, ii. Advanced (stage 4-5) chronic kidney disease or dialysis therapy, Severe liver  
29 161 damage (Child-Pugh score C, AST> 5 times the upper limit), HIV, (5) Gout/history of Gout or  
30 162 hyperuricemia (two times above the ULN), (6) Having used Favipiravir or participated in any  
31 163 other interventional drug clinical study within 30 days prior to first dose of study drug, (7)The  
32 164 investigator believes that participating in the trial is not in the best interests of the patient, or the  
33 165 investigator considers unsuitable for enrollment (such as unpredictable risks or subject  
34 166 compliance issues), (8) Clinical prognostic non-survival, palliative care, or in deep coma and no  
35 167 have response to supportive treatment within three hours of admission.

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46 **168 Definitions:**

47 169 Mild COVID-19 cases are defined as patient presenting with a mild illness, (absent or mild  
48 170 pneumonia), oxygen saturation >94% at room air; and does not require ICU admission.

49 171 Mild illness may include: uncomplicated upper respiratory tract viral infection symptoms such as  
50 172 fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore

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3 173 throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea,  
4 174 nausea, and vomiting.

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6 175 Viral clearance is defined as polymerase chain reaction (PCR) negative results.  
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## 10 177 **Outcome measurements**

### 11 178 **Primary outcome**

12 179 To evaluate the effect of Favipiravir on the timing of PCR test conversion from positive to  
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14 180 negative within 15 days after starting medicine.

### 15 181 **Secondary Objectives**

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18 182 ➤ To evaluate Favipiravir's effect on clinical recovery.  
19  
20 183 ➤ Evaluate symptoms severity and the progression in the disease course in both arms till 28  
21 184 days after starting medicine.  
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23 185 ➤ To evaluate Favipiravir's effect on the requirement of the use of antipyretics, analgesics, or  
24 186 antibiotics within 15 days after starting medicine.  
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26 187 ➤ To evaluate Favipiravir's effect on disease complications within 28 days after starting  
27 188 medicine (hospitalization, ICU admission or Mechanical ventilation).  
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29 189 ➤ Evaluate the safety of investigational therapeutics as compared to the control arm within 15  
30 190 days after starting medicine.  
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### 35 191 **Other Variables**

36 192 Data will also be collected on demographic and epidemiological factors like (age, gender and  
37 193 ethnic group), co-morbidities, vital signs and symptoms at presentation, laboratory findings  
38 194 ( CBC, liver function, kidney function ,potassium, sodium, glucose and chest X-ray), any  
39 195 hospitalization during enrollment period and concomitant medications.  
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### 44 196 **Study Procedures**

45 197 The Study comprises three major parts screening, treatment and follow-up period. Each part  
46 198 consists of specified procedures to be done and assessments to be carried. The investigator and  
47 199 supporting study team will be responsible to document all the procedures and assessments done  
48 200 in the appropriate source document and the patient e-CRFs. All procedures and assessments will  
49 201 support the safety and validity of conclusions drawn from the study protocol. Procedures and  
50 202 assessments such as vital signs, laboratory test, will follow in-house policies and guidelines.  
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203 When multiple assessments are taken at the same time point, the most out-of-range value shall be  
204 considered. Table 1 describes the different stages of the study and tasks to be completed.

### 205 **Screening/Baseline**

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

### 211 **Randomization**

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

### 217 **Treatment Period**

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

### 222 **Treatment compliance**

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

### 226 **Follow-up Period**

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

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

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

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3 233 obtaining specimens will be done through a mobile team trained as per study protocol or in an  
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5 234 outpatient clinic.

6 235 Follow-up of symptoms evaluation should be for 15 days or until patient reaches secondary  
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8 236 endpoint (resolving symptoms).

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10 237 **PARTICIPANT DISCONTINUATION**

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12 238 Premature discontinuation of the trial would be based on the decision of DSMB or the  
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14 239 investigator initiated based on the following:

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16 240 - Adverse event: clinical or laboratory event that in the medical judgment of the investigator,  
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18 241 for the best interest of the patient are grounds for discontinuation
- 19 242 - A major deviation from the protocol: the patient's findings or conduct failed to adhere to the  
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21 243 protocol requirements.
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23 244 - Other reasons: e.g., an administrative problem such as termination of study by the sponsor.  
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263 **Table 1-Flow chart**

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

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## 268 STATISTICAL CONSIDERATIONS

### 269 General Considerations

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

### 276 Sample Size and Power Considerations

277 Assumptions and Study Hypothesis:

- 278 **a.** The current study's primary hypothesis is  $H_0: HR = 1$  vs.  $H_1: HR \neq 1$ ; and HR is  
279 the hazard ratio of treatment compared to control arm.
- 280 **b.** Time to viral clearance  
281 In patients with mild COVID19, 90% of the patients clear the virus by day 10 of  
282 onset.(1) If we assume an exponential hazard, we estimate the median time of  
283 viral clearance in the placebo group to be 8 days.
- 284 **c.** The exact treatment effect from Favipiravir is not known but can be approximated  
285 using prior clinical studies. A study comparing Favipiravir's effect to  
286 lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral  
287 clearance in the Favipiravir arm.(6) To stay on the conservative side, we assume  
288 that Favipiravir will reduce the median time to virus clearance to 6 days which is  
289 equivalent to hazard ratio of 1.33.
- 290 **d.** We further assume that 90% of the control group patients will have viral  
291 clearance within 15 days, and 90% will have viral clearance in the treatment arm.
- 292 **e.** It is anticipated that very few of these subjects will be randomized and not start  
293 study treatment (and so be excluded from the primary analysis) or be lost to  
294 follow-up (and so have missing data for the primary endpoint). Given certain  
295 uncertainties however, we have included a nominal 10% drop out rate.

### 296 Sample Size Estimation for Classical Two Arm Parallel Design:

297 Under the classical two arm parallel design, a one-sided test of whether the hazard ratio is 1 with  
 298 an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the  
 299 treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is  
 300 1.330. The number of events (i.e., subjects with viral clearance) required to achieve this power is  
 301 517.5. The proportions of events during the study are anticipated to be 0.900 for the control  
 302 group and 0.900 for the treatment group. We anticipate 10% drop out rate and therefore we  
 303 expect that the trial will recruit 317 subjects per arm. These results assume that the hazard ratio is  
 304 constant throughout the study and that Cox proportional hazards regression is used to analyze the  
 305 data.

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

311 Boundary

312 **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

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

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$$N = \left(\frac{E_0}{E}\right)^a N_0$$
  
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7 320 where 'a' is a constant which will be set to 2 and 'N'<sub>0</sub> is a number chosen to be slightly larger  
8 321 than the classical sample size per group, E<sub>0</sub> is the planned effect size of 1.33, and E is the  
9 322 observed effect size from the interim analysis.

### 13 323 **Patient and Public involvement**

15 324 It was not appropriate or possible to involve patients or the public in the design of the study  
16 325 The results of the study will be disseminated to the public via social media platforms.  
17 326

### 20 327 **Ethics**

22 328 This study will be carried out in compliance with the protocol and by the laws and regulations of  
23 329 King Abdullah International medical research Centre ethics committee (KAIMRC IRB). The  
24 330 study will adhere to the principles of Good Clinical Practice that it conforms to a copy of the  
25 331 Declaration of Helsinki. This study was approved by KAIMRC IRB with protocol number  
26 332 RC20/220. The authors will seek approval for protocol amendments, which will be reported to  
27 333 the clinical trials registration site.  
28 334

### 35 335 **CONFIDENTIALITY AND DATA MANAGEMENT**

37 336 The research coordinator with expertise in data entry will enter data into a password-protected  
38 337 database. Data will be entered and double checked for accuracy. After resolving of any  
39 338 discrepancies and a combination of manual and automated data- review procedures, the final data  
40 339 set will be subject to a quality assurance audit.

44 340 A clinical data management review will be performed on all subject data to ensure clinical data  
45 341 quality across all participants and sites. During this review, subject data will be checked for  
46 342 consistency, omissions, and any apparent discrepancies. Also, the data will be reviewed for  
47 343 adherence to the protocol. During data analysis, non-identifiable data will be provided in a  
48 344 password protected excel sheet.



### 345 **Data Safety Monitoring Board**

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

### 350 **Discussion**

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

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

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

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

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

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3 375 China, 37.8% USA accounting for 87.6% studies from both countries. From the 201 trials only  
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5 376 11 trials are being done on Favipiravir.(10)

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7 377 As of the 23rd of July, 2020; there are 32 studies registered on [clinicaltrials.gov](https://clinicaltrials.gov) to assess the  
8  
9 378 utility of this drug in the management of COVID-19 (3 completed, 12 recruiting).

10 379 (11) Currently there are only two countries (KSA and Kuwait) from Middle East with ongoing  
11  
12 380 trials on Favipiravir with placebo comparator. (12) Our study is the first trial registered from the  
13  
14 381 Middle East region till date funded by the Government of KSA. Recently a study was done in  
15  
16 382 India on Favipiravir in mild to moderate COVID 19 Cases. This was an randomized open label  
17  
18 383 study and the sample size of only 150 patients (13) . There are certain limitations reported in this  
19  
20 384 study which were due to small sample size the hazards ratio reported was small and due to open  
21  
22 385 label nature of the study it may have been subjected to potential bias. The primary endpoint in  
23  
24 386 this study was confounded due to interpretation issues with RT-PCR positivity and its lack of  
25  
26 387 correlation with clinical cure. (13)

27 388 Our study it is a double blind; placebo controlled randomized study which provides high quality  
28  
29 389 evidence. The sample size in our study is 576 subjects, which is the largest second to the trial in  
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31 390 Kuwait (780) from the presently ongoing trials on Favipiravir.(12) The design of the study  
32  
33 391 eliminates potential bias and the large sample size helps to obtain a hazards ratio of 1.

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### 393 **Limitations:**

36 394 Numerous challenges are expected during this trial. The trial is ongoing now during restricted  
37  
38 395 travel time, and hospitals restricted nonessential personnel's entry. Protocol training, site  
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40 396 initiation visits, and monitoring visits will be performed remotely in many sites. The research  
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42 397 team will be assigned to other clinical services, and many members require extra effort. Also,  
43  
44 398 study team member's sicknesses or unprotected exposure to COVID-19 patient strained research  
45  
46 399 resources. Many sites may encounter inadequate supplies of personal protective equipment and  
47  
48 400 trial-related supplies.

### 401 **Author Contributions:**

49  
50 402 MoB, AhH, MoA, KhS, AbM, HaQ, MaS, EbM, AdA, AbA, SaA, MaJ, and AhA participated in  
51  
52 403 study design and protocol development. MoB, AbM, KhA, KhS, AbA are involved in subject  
53  
54 404 recruitment and follow-up plan. MoH, OmA, AhA, and MoB participated in the development of  
55  
56 405 statistical analysis plan. KhS, MoB, AbA, and AhH contributed to manuscript preparation. KhS  
57  
58 406 and MoB contributed to review and manuscript submission.

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3 4074 408 **Funding:**5 409 This work was supported by King Abdullah International Research Centre, KSA (grant no.  
6 410 RC20/220/R).

7 411

8 412 **Competing interests:**

9 413

10 414 Authors declare no competing interest.

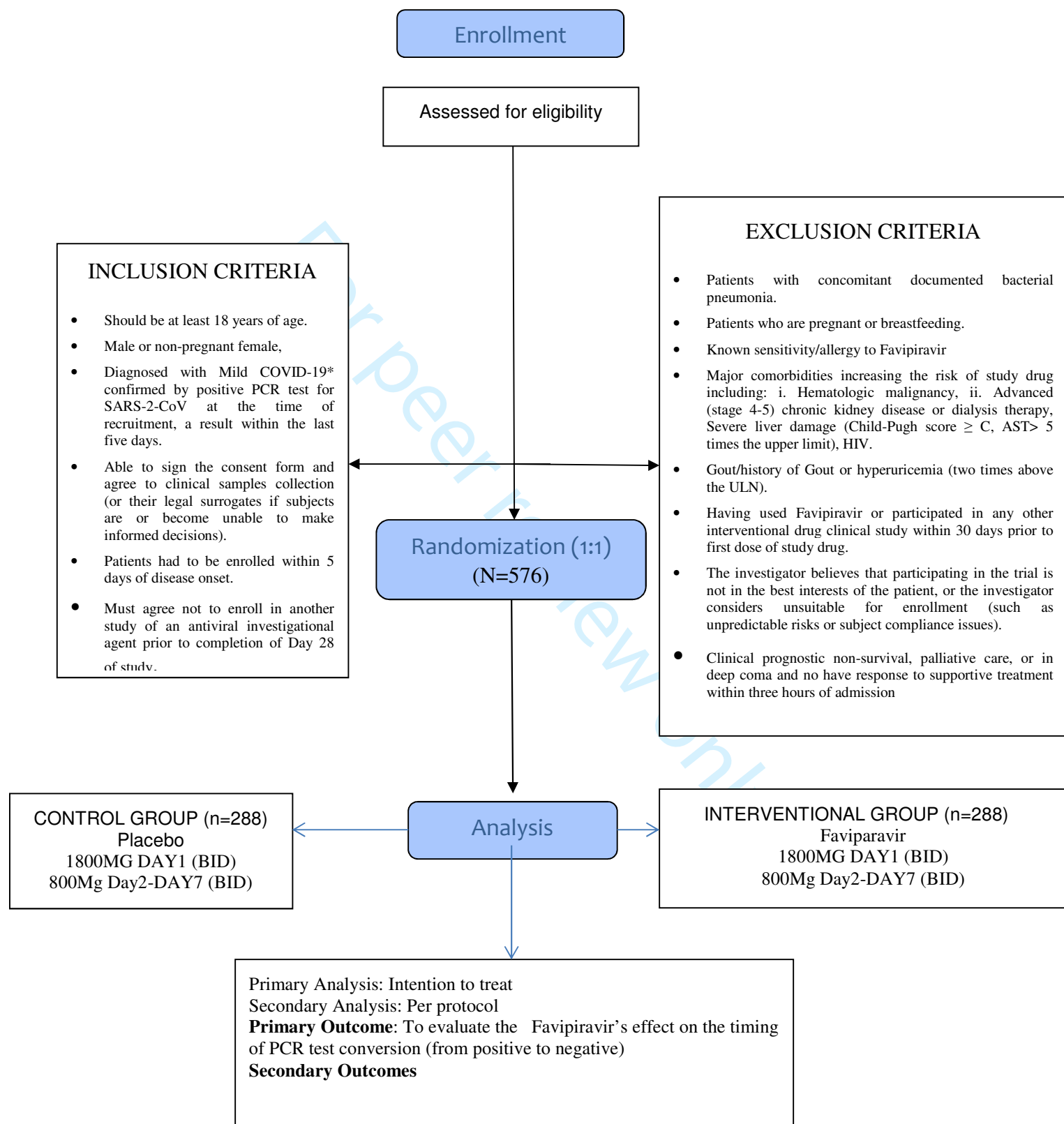
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15 416 **REFERENCES**

- 16  
17 417 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  
18 418 COVID-19. *The Lancet Infectious Diseases*. 2020;20(6):656-7.
- 19 419 2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease  
20 420 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for  
21 421 Disease Control and Prevention. *JAMA*. 2020.
- 22 422 3. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for  
23 423 Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 2016;123(6):1386-  
24 424 94.
- 25 425 4. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and  
26 426 emerging RNA viruses. *Antiviral research*. 2018;153:85-94.
- 27 427 5. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA  
28 428 polymerase. *Proceedings of the Japan Academy Series B, Physical and biological sciences*.  
29 429 2017;93(7):449-63.
- 30 430 6. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for  
31 431 COVID-19: An Open-Label Control Study. *Engineering (Beijing, China)*. 2020.
- 32 432 7. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A  
33 433 Randomized Clinical Trial. *medRxiv*. 2020:2020.03.17.20037432.
- 34 434 8. James MI. Preliminary report of favipiravir observational study in Japan released. online: News-  
35 435 Medical.net, 2020.
- 36 436 9. Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered  
37 437 with ClinicalTrials.gov: cross-sectional analysis. *BMJ Open*. 2020;10(9):e041276.
- 38 438 10. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical  
39 439 trials assessing treatments for COVID-19: a cross-sectional analysis. *BMJ Open*. 2020;10(6):e039978.
- 40 440 11. Agrawal U, Raju R, Udawadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19.  
41 441 *Med J Armed Forces India*. 2020;76(4):370-6.
- 42 442 12. Listed COVID 19 Studies [Internet]. online: US National Institute of Health (NIH); 2020 [cited 2020  
43 443 26 Nov]. *Clinicaltrials.org*. Available from: <https://www.clinicaltrials.gov>.
- 44 444 13. Udawadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and Safety of  
45 445 Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A  
46 446 Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial. *International Journal of*  
47 447 *Infectious Diseases*. 2020.

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Figure 1. 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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3 and 5
<b>Methods</b>			
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
<b>Randomisation:</b>			
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

1				
2	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
3				NA
4		11b	If relevant, description of the similarity of interventions	10
5	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
6		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
7				
8	<b>Results</b>			
9	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
10		13b	For each group, losses and exclusions after randomisation, together with reasons	NA
11	Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
12		14b	Why the trial ended or was stopped	NA
13	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
14	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
15				
16	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
17		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
18	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
19				
20	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
21				
22	<b>Discussion</b>			
23	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
24	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
25	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
26				
27	<b>Other information</b>			
28	Registration	23	Registration number and name of trial registry	2
29	Protocol	24	Where the full trial protocol can be accessed, if available	2
30	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2
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43	CONSORT 2010 checklist			
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\*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](http://www.consort-statement.org).

For peer review only

# BMJ Open

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

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

## Title Page

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

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4 47  
5 48 **Abstract:**  
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7 50 **Introduction**  
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9 52 A novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of  
10 53 respiratory illness termed COVID-19 in Dec 2019. There is a lack of specific therapeutic agents  
11 54 based on evidence for this novel coronavirus infection; however, several medications have been  
12 55 evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients and decrease  
13 56 virus carriage duration to limit the community's transmission..

14 57 **Methods and Analysis**  
15 58

16 59 We hypothesize that mild COVID-19 patients treated with Favipiravir will have a shorter  
17 60 duration of time to virus clearance than the control group. The primary outcome is to evaluate  
18 61 the effect of Favipiravir on the timing of PCR test conversion from positive to negative within 15  
19 62 days after starting the medicine.

20 63 Adults (>18 years, male or non-pregnant female, diagnosed with mild COVID-19 within five  
21 64 days of disease onset) are being recruited by physicians participating from the Ministry of  
22 65 National Guard Health Affairs(MNGHA) and Ministry of Health(MOH) ethics committee  
23 66 approved primary health care centers. This double-blind, randomized trial comprises three  
24 67 significant parts screening, treatment, and follow-up period, where treating physician and  
25 68 patients are blinded. Eligible participants will be randomized in a 1:1 ratio to either the therapy  
26 69 group (Favipiravir) or a control group (Placebo) with 1800 mg by mouth twice daily for the first  
27 70 day, followed by 800mg twice daily for 4-7 days. Serial nasopharyngeal/Oropharyngeal swab  
28 71 samples will be obtained on day 1(-5 days before therapy). On day's 5±1 day, 10±1day,  
29 72 15±2days, extra nasopharyngeal/ Oropharyngeal PCR COVID-19 samples will be requested.  
30 73 The primary analysis population for evaluating both efficacy and safety outcomes will be a  
31 74 modified ITT population. Anticipating a 10% drop-out rate, we expect to recruit 288 subjects per  
32 75 arm. The results assume that the hazard ratio is constant throughout the study and that Cox  
33 76 proportional hazards regression is used to analyze the data.  
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## **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

## 112 Introduction

113 In December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international  
114 outbreak of respiratory illness termed COVID-19. The WHO declared the epidemic of COVID-  
115 19 as a pandemic on 12th March 2020. (1) According to a recent Chinese study, “about 80% of  
116 patients present with mild disease, and the overall case-fatality rate is about 2.3% but reaches  
117 8.0% in patients aged 70 to 79 years”. (2) Mild cases have been found to have viral loads 60-fold  
118 less than severe cases. The viral loads of asymptomatic individuals are lower, with possible  
119 implications for infectiousness and diagnosis. (3) In Saudi Arabia, as of 27th March 2020, 1012  
120 confirmed cases of the disease were reported. (4) There are no specific therapeutic agents based  
121 on substantial evidence for these novel coronavirus infections; however, several medications  
122 have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients  
123 and decrease virus carriage duration to limit the community’s transmission.

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

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

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

## 143 **Research hypothesis**

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

## 146 **Methods and analysis**

### 147 **Study Design**

148 AviMild is a phase III randomized double-blinded placebo-controlled parallel-group multicenter  
149 clinical trial to evaluate Favipiravir's safety and efficacy in adults diagnosed with mild COVID-  
150 19. The trial involves patients from the community settings from different cities in Saudi Arabia  
151 with King Abdullah International Medical Research Center (KAIMRC) as the sponsor. The  
152 protocol described in this article is V2.2 approved on 20 Nov 2020. This RCT has been  
153 developed according to the Standard Protocol Items: Recommendations for Intervention Trials  
154 2013 statement. (14)

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

### 164 **Study Population**

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

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3 173 Riyadh, MNGHA Madinah and PHC Safiyah -Madinah, King Fahad Hospital -Madinah, King  
4 174 Abdullah Medical City- Makkah..

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6 175 The sponsor has subscribed an insurance policy covering the sponsor's own third-party liability  
7 176 as well as the third-party liability of all the investigators involved for the study's duration.

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### 11 178 Inclusion Criteria

12 179 Patients must be eligible according to the following criteria for enrollment

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14 181 (1) Should be at least 18 years of age

15 182 (2) Male or non-pregnant female (pregnancy testing is not mandatory. If the patient requests or is  
16 183 not sure, the study team will provide it)

17 184 (3) Diagnosed with mild COVID-19\* confirmed by positive PCR test for SARS-CoV-2 at the  
18 185 time of recruitment, a result within the last five days

19 186 (4) Patients have to be enrolled within 5 days of disease onset.

### 20 187 Exclusion criteria

21 188 Patients meeting any of the following criteria will be excluded from trial enrolment:

22 189 (1) Patients with concomitant documented bacterial pneumonia established through positive  
23 190 sputum cultures

24 191 (2) Patients who are pregnant or breastfeeding

25 192 (3) Known sensitivity/allergy to Favipiravir (If Favipiravir was used for COVID-19 in the  
26 193 patient previously for influenza)

27 194 (4) Major comorbidities increasing the risk of study drug including

- 28 195
- 29 196 • Hematologic malignancy
  - 30 197 • Advanced (stage 4-5) chronic kidney disease or dialysis therapy
  - 31 198 • Severe liver damage (Child-Pugh score C, AST> 5 times the upper limit)
  - 32 199 • HIV
  - 33 200 • Gout/history of Gout or hyperuricemia (two times above the ULN)

34 201 (6) Having used Favipiravir or participated in any other interventional drug clinical study within  
35 202 30 days before the first dose of study drug (i.e., the patient received it for influenza previously)

36 203 (7) The investigator believes that participating in the trial is not in the best interests of the  
37 204 patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or

38 205 subject compliance issues)



1  
2  
3 205 (8) Clinical prognostic non-survival, palliative care, or in a deep coma and have no response to  
4  
5 206 supportive treatment within three hours of admission.

6  
7 207 (9) Hospitalized patients for moderate or severe COVID-19

8  
9 208 **Definitions:**

10 209 a. Mild COVID-19 cases are defined as a patient presenting with a mild illness (absent or mild  
11  
12 210 pneumonia), oxygen saturation >94% at room air, and not requiring ICU admission.

13 211 Mild illness may include uncomplicated upper respiratory tract viral infection symptoms such as  
14  
15 212 fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore  
16  
17 213 throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea,  
18  
19 214 nausea, and vomiting.

20 215 b. Viral clearance is defined as polymerase chain reaction (PCR) negative results.

21  
22 216 **Randomization**

23  
24 217 Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or  
25  
26 218 a control group (placebo). The randomization list is computer generated and is stratified by  
27  
28 219 clinical site. The patients will be randomized, utilizing an electronic case report (e-CRF) form  
29  
30 220 (REDCAP) to ensure allocation concealment. The sequence of treatment assignments will be  
31  
32 221 determined before the start of the study.

33 222 **Blinding**

34  
35 223 The trial is double-blind, meaning that the participants, investigators, and other study staff are  
36  
37 224 unaware of the treatment assignment. The Sponsor's investigational drug unit, not part of the  
38  
39 225 study team holds the information for treatment allocation.

40 226 **Rationale for study treatment**

41  
42 227 Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase. It acts as a  
43  
44 228 purine analog, which selectively inhibits viral RNA-dependent RNA polymerase (RdRps).

45 229 Favipiravir has the characteristic of acting on RNA viruses, including Ebola and Coronaviruses  
46  
47 230 especially, novel coronavirus. For the Ebola virus, favipiravir effectively prevented Ebola in  
48  
49 231 mice by 100%, although EC<sub>50</sub> (drug concentration was found to reduce viral replication by  
50  
51 232 50%) ~67 μM. A recent in vitro study on clinical isolates of COVID-19 showed that Favipiravir  
52  
53 233 has EC<sub>50</sub> =61.88μM. (15) ). The dose was chosen based on the drug insert (Fabiflu Prescribing  
54  
55 234 Information) provided for the medication from the studies that were done in Japan and according  
56  
57 235 to the published studies.(13, 16)

236

## 237 Participant Timeline

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

### 248 **Screening/Baseline: Day -1 to Day1**

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

### 258 **Treatment Period: DAY 1**

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

## 265 Treatment compliance

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

## 270 Follow-up Period-Day1-15 and Day 28

271 The follow-up period starts from the second day after randomization for 14 days, where the  
 272 research coordinator or the physician will follow-up the patient's health through a phone call.  
 273 Follow-up of symptoms evaluation should be for 15 days or until the patient reaches the  
 274 secondary endpoint (resolving symptoms). The patient's assessment will be recorded in the e-  
 275 CRF. Another follow-up will be made on day 28 days from randomization. On day's 5±1 day,  
 276 10±1day, 15±2days, extra nasopharyngeal/ oropharyngeal PCR COVID-19 samples will be  
 277 requested by delegated specialist trained clinical personnel part of the research team, and results  
 278 documented in e-CRF. Patients' follow-up and needed laboratory investigations will be done  
 279 while the patient is in the hospital. If the patient is discharged or in outpatient settings, the  
 280 follow-up evaluation and obtaining specimens will be done by delegated personnel in the  
 281 outpatient clinic or mobile team trained as per study protocol.

282 **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	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										

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

285

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

### 289 Primary outcome

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

### 292 Secondary Objectives

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

306

## 307 PARTICIPANT DISCONTINUATION

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

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

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

### 315 Data collection, management and Analysis

316  
317 The research coordinator with expertise in data entry will enter data into a password-protected  
318 database (REDCAP). All observations and other data pertinent to the clinical investigation will  
319 be recorded into the e-CRF. Data will be entered and double-checked for accuracy. After  
320 resolving any discrepancies and a combination of manual and automated data-review procedures,  
321 the final data set will be subject to a quality assurance audit.

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

### 328 Safety and adverse events monitoring

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

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

- 1  
2  
3 336           ○ Moderate: discomfort noted of sufficient severity to reduce or adversely affect  
4  
5 337           normal activity.  
6  
7 338           ○ Severe: incapacitating, with the inability to work or perform normal daily activity.  
8  
9 339       • The assessment of the relationship of adverse event (AE) to study medication, i.e.,  
10  
11 340       according to the definitions below:  
12  
13 341           ○ Related: with a reasonable causal relationship to the investigational product.  
14  
15 342           ○ Not Related: without a reasonable causal relationship to the investigational  
16  
17 343           product.  
18  
19 344           ○ Other: in such a case, the investigator's causality assessment should be specified.  
20  
21 345       • Description of action taken in treating the AE and/or change in study medication  
22  
23 346       administration or dose.

24  
25 347 As far as possible, all investigators will follow-up participants with AEs until the event is  
26  
27 348 resolved or until, in the investigator's opinion, the event is stabilized or determined to be chronic.  
28  
29 349 Details of AE resolution will be documented in the e-CRF. Any significant changes in AEs will  
30  
31 350 be reported even though the subject has completed the study, including the protocol-required  
32  
33 351 post-treatment follow-up.

## 34 352 **Statistical methods:**

### 35 353 **General Considerations**

36  
37 354 This is a randomized, double-blinded study comparing Favipiravir tablets to placebo group to  
38  
39 355 treat subjects with mild SARS-CoV-2 infection. The Intention to treat (ITT) analysis will include  
40  
41 356 all subjects randomized which will ignore noncompliance, protocol deviations, withdrawal, and  
42  
43 357 anything that will take place after randomization. (17, 18) The primary analysis population for  
44  
45 358 evaluating both efficacy and safety outcomes will be a modified ITT population, and will include  
46  
47 359 all subjects who have been randomized but will exclude some randomized subjects like patients  
48  
49 360 who were judged ineligible after randomization or patients who withdrew consent or certain  
50  
51 361 patients who never started treatment (17, 18), study drug (Favipiravir tablets or Placebo) was  
52  
53 362 started, and the patient did not withdraw consent. These results assume that the hazard ratio is  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 363 constant throughout the study and that Cox proportional hazards regression is used to analyze the  
4  
5 364 data.

## 6 365 Sample Size and Power Considerations

### 7 366 Assumptions and Study Hypothesis:

8  
9  
10  
11 367 **a.** The current study's primary hypothesis is  $H_0: HR = 1$  vs.  $H_1: HR \neq 1$ ; and HR is  
12  
13 368 the hazard ratio of treatment compared to control arm.

14 369 **b.** Time to viral clearance

15  
16 370 In patients with mild COVID-19, 90% of the patients clear the virus by day 10 of  
17  
18 371 onset.(1) If we assume an exponential hazard, we estimate the median time of  
19  
20 372 viral clearance in the placebo group to be 8 days.

21 373 **c.** The exact treatment effect from Favipiravir is not known but can be approximated  
22  
23 374 using prior clinical studies. A study comparing Favipiravir's effect to  
24  
25 375 lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral  
26  
27 376 clearance in the Favipiravir arm.(19) To stay on the conservative side, we assume  
28  
29 377 that Favipiravir will reduce the median time to virus clearance to 6 days which is  
30  
31 378 equivalent to hazard ratio of 1.33.

32 379 **d.** We further assume that 90% of the control group patients will have viral  
33  
34 380 clearance within 15 days, and 90% will have viral clearance in the treatment arm.

35 381 It is anticipated that very few of these subjects will be randomized and not start  
36  
37 382 study treatment (and so be excluded from the primary analysis) or be lost to  
38  
39 383 follow-up (and so have missing data for the primary endpoint). Given certain  
40  
41 384 uncertainties however, we have included a nominal 10% drop out rate.

### 42 385 Sample Size Estimation for Classical Two Arm Parallel Design:

43  
44  
45 386 Under the classical two-arm parallel design, a one-sided test of whether the hazard ratio is 1 with  
46  
47 387 an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the  
48  
49 388 treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is  
50  
51 389 1.330.

52 390 The sample size re-estimation will be based on the ratio of the planned effect size (1.33) to the  
53  
54 391 observed effect size from the interim analysis according to the following formula:

1  
2  
3  
4 392 
$$N = \left(\frac{E_0}{E}\right)^a N_0$$
  
5  
6

7 393 where 'a' is a constant which will be set to 2 and is a number chosen to be slightly larger than the  
8 394 classical sample size per group, is the planned effect size of 1.33, and E is the observed effect  
9 395 size from the interim analysis.

12 396 A detailed statistical analysis plan will be developed before undertaking any comparative  
14 397 analyses of outcomes. The following provides a summary of the approach to analysis for the  
15 398 primary endpoint.

17  
18 399 Analysis of the primary endpoint:

19  
20 400 The primary endpoint of the current study is the rate of viral clearance. The number and percent  
21 401 of subjects who met the endpoint by day 15 of follow up will be calculated and tabulated. Due to  
22 402 the nature of the data collection (i.e., subjects clearance will be observed during specific follow-  
23 403 up time), survival analysis methods for interval-censored data will be used to analyze the data.  
24  
25 404 All results will be reported in H.R and the corresponding lower confidence limit and one-sided p-  
26  
27 405 value.

28  
29  
30 406 For secondary endpoints:

- 31  
32 407
- 33 408 • Quantitative variables such as 'change from baseline in clinical scores' are expected to  
34 409 have reasonably skewed distributions. They may be subject to censoring, e.g., for  
35 410 subjects in hospital on day 28, compared between randomized arms using non-parametric  
36 411 tests (Wilcoxon's test).
  - 37 412 • Analysis of the other secondary endpoints will use a proportional odds model with an  
38 413 indicator variable for randomized treatment. The Wald test will generate a p-value  
39 414 comparing treatments and the estimated proportional odds ratio comparing treatments  
40 415 with associated 95% CI.
  - 41 416 • Analysis of AE data will primarily be descriptive based on MedDRA coding of events.  
42 417 The proportion of subjects experiencing an SAE and the proportion experiencing a  
43 418 Grade
  - 44 419 • Three or higher AEs will be compared between randomized arms using Fisher's Exact  
45 420 Test.
- 46  
47  
48  
49  
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57



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

424 **Data Monitoring:**

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

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

436 **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

437

438 **Frequency and procedures for auditing trial conduct:**

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

## 442 **Ethics**

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

## 458 **Discussion**

459 During the Ebola virus disease outbreak, the JIKI trial illustrated an improved survival rate in  
460 patients with moderate to high viral load with favipiravir. (21) Similarly, Bai et al.'s study  
461 proved a significant decline in viral load with favipiravir in patients with moderate viral load at  
462 baseline. (22) These findings support the role of favipiravir in viral load reduction. Since the  
463 homology of gene sequences of SARS-CoV-2 and SARS was over 90%, it is expected that the  
464 intervention of antiviral drugs in COVID-19 patients will likely improve or shorten the time to  
465 viral clearance. (23) The reduction in time to viral clearance is chosen as the endpoint based on  
466 the above evidence. Therefore, viral clearance, which captures the viral shedding duration and  
467 possible contagiousness period, reflects the best assessment. Several published trials have  
468 studied similar endpoints as our study due to their clinical significance. A study of 80 patients  
469 with COVID-19 compared Favipiravir to lopinavir/ritonavir. The study reported a shorter viral  
470 clearance time for the Favipiravir arm versus the lopinavir/ritonavir arm median 4 days (IQR:  
471 2.5–9) versus 11days (IQR: 8–13),  $P < 0.001$ ). Multivariable Cox regression showed that  
472 favipiravir was significantly ( $p = 0.026$ ) associated with faster viral clearance. Additionally the

1  
2  
3 473 timing of antiviral therapy reached near significance ( $p = 0.055$ ). (19) Furthermore, it was  
4 474 superior to Arbidol in having a higher 7-day clinical recovery rate in patients with COVID-19  
5 475 and a more significant reduction in fever and cough (15). A Japanese observational study  
6 476 assessed the safety and efficacy of favipiravir. The median duration of therapy was 11 days, with  
7 477 reported clinical improvement rates at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%,  
8 478 and 40.1% and 60.3% for mild, moderate, and severe disease, respectively. (24) A prospective,  
9 479 randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-  
10 480 19 chose the primary endpoint was viral clearance by day 6. The secondary endpoint was a  
11 481 change in viral load by day 6. Additionally, exploratory endpoints included time to  
12 482 defervescence and resolution of symptoms. (25) A trial from Russia enrolled 60 patients (40 on  
13 483 favipiravir and 20 on Supportive Care) with primary endpoint as viral elimination. The  
14 484 secondary endpoints were defervescence and RT-PCR negativity. (13) Lately, a phase 3, open-  
15 485 label, randomized, multicenter study (Glenmark Pharmaceuticals) was initiated in India. The  
16 486 primary endpoint was time until the cessation of oral shedding of the SARS-CoV-2 virus. (26)  
17 487 According to a study by Jones et al., there are 630 registered trials for COVID-19 on the  
18 488 clinicaltrials.gov website by 1 May, 2020. Most of these trials are from Europe, the USA, China,  
19 489 and other Asian countries. Additionally, all the trials on the drugs or biologics (218) are studying  
20 490 drugs like hydroxychloroquine or chloroquine (88), azithromycin (53), and 25 trials assessing  
21 491 convalescent plasma, lopinavir/ ritonavir, stem cell treatments, and tocilizumab. (27)

22 492  
23  
24 493 Another study reported 201 trials registered with the US registry and WHO clinical trials  
25 494 registry platform. Out of these, 93.5% studied drug intervention. From the total trials, 49.8%  
26 495 were from China, 37.8% USA accounting for 87.6% of both countries studies. From the 201  
27 496 trials, only 11 trials are being done on Favipiravir. (28) As of 23 July 2020, there are 32 studies  
28 497 registered on clinicaltrials.gov to assess this drug's utility in the management of COVID-19 (3  
29 498 completed, 12 recruiting). (29)

30 499 Many clinical trials conducted in China, Japan, Russia, and India had an open-label design,  
31 500 which leads to reporting biased results. (13, 19, 25, 26) Recently a study was done in India on  
32 501 Favipiravir in mild to moderate COVID-19 Cases. This was a randomized, open-label study and  
33 502 the sample size of only 150 patients. (30) There are certain limitations reported in this study,  
34 503 which were due to the small sample size. The hazard ratio reported was small, and due to the

1  
2  
3 504 study's open-label nature, it may have been subjected to potential bias. This study's primary  
4  
5 505 endpoint was confounded due to interpretation issues with RT-PCR positivity and its lack of  
6  
7 506 correlation with the clinical cure. (30)

8 507 A systemic review and meta-analysis of Favipiravir reported evidence showing potential benefits  
9  
10 508 of this drug in clinical and imaging improvement after treating COVID-19 patients. Therefore  
11  
12 509 there is a need for additional randomized, double-blind clinical trials to form a definite opinion  
13  
14 510 about the rationale to use this drug. There were several drawbacks to the studies that have  
15  
16 511 already been published, such as non-randomized design, small sample sizes, and different  
17  
18 512 durations of treatment, different dosage regimes, and lack of blinding. (31)

19 513  
20 514 In our study, we adopted the design double-blind, placebo-controlled randomized study, which  
21  
22 515 provides the best evidence of causation. (32) Randomized double-blind placebo control studies  
23  
24 516 (RDPCS) are regarded as the “gold standard” of epidemiologic studies. They are employed to  
25  
26 517 illustrate superiority, equivalence, and non-inferiority. Well-designed RDPCS gives the most  
27  
28 518 robust possible evidence of causation. The benefits of randomization are 1. It avoids selection  
29  
30 519 bias that may happen if either the physician or the patient decides the treatment, 2. It removes  
31  
32 520 most confounding by all known and unknown factors as it prevents an association between the  
33  
34 521 treatment and any other known or unknown factor. Blinding with randomization evades  
35  
36 522 reporting bias as no one is aware of the treatment; hence all treatment groups will be treated the  
37  
38 523 same. The use of placebo as control leads to the placebo effect where the person on placebo will  
39  
40 524 think that they are taking the actual treatment, which leads them to feel better or respond to it due  
41  
42 525 to wishful thinking. The presence of placebo control will help to compare the drug's  
43  
44 526 effectiveness against the placebo's effectiveness (33-35)

45 527 There are currently only two countries (KSA and Kuwait) from the Middle East with ongoing  
46  
47 528 Favipiravir trials with a placebo comparator. (29) Our study is the first trial registered from the  
48  
49 529 Middle East region to date funded by the government of KSA. Our study's sample size is 576  
50  
51 530 subjects, the second largest to Kuwait's trial (780) from the presently ongoing Favipiravir  
52  
53 531 trials.(29) .

### 54 532 **Limitations:**

55 533 Numerous challenges are expected during this trial. The trial is ongoing now during restricted  
56  
57 534 travel time, and hospitals restricted nonessential personnel's entry. Protocol training, site

1  
2  
3 535 initiation visits, and monitoring visits will be performed remotely in many sites. The research  
4  
5 536 team will be assigned to other clinical services, and many members require extra effort. Also,  
6  
7 537 study team member's sicknesses or unprotected exposure to COVID-19 patient strained research  
8  
9 538 resources. Many sites may encounter inadequate supplies of personal protective equipment and  
10  
11 539 trial-related supplies. The study is prone to certain biases due to the design, such as non-  
12 540 compliance, withdrawals after randomization, and attrition/losses to follow-up.

13 541

#### 15 542 Trial status

17 543 This trial began on 23 July 2020. On 27 Jan 2021, 160 patients have been included.

19 544

#### 21 545 Data sharing plan

23 546 Study protocol and statistical plan will be openly available.

24 547

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33 552

#### 34 553 Author Contributions:

36 554 MoB, AhH, MoA, KhS, AbM, HaQ, MaS, EbM, AdA, AbA, SaA, MaJ, and AhA participated in  
37  
38 555 study design and protocol development. MoB, AbM, KhA, KhS, AbA are involved in subject  
39  
40 556 recruitment and follow-up plan. MoH, Oma, AhA, and MoB participated in the development of  
41  
42 557 statistical analysis plan. KhS, MoB, AbA, and AhH contributed to manuscript preparation. KhS  
43  
44 558 and MoB contributed to review and manuscript submission.

45 559

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50 563

#### 51 564 Competing interests:

52 565 Authors declare no competing interest.

53 566

54 567

## 568 Patient and Public involvement

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

571  
572 Figure 1 Overview of Study

573  
574 Figure 2 Schedule of Enrollment

## 575 REFERENCES

- 576 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  
577 COVID-19. *The Lancet Infectious Diseases*. 2020;20(6):656-7.
- 578 2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease  
579 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for  
580 Disease Control and Prevention. *JAMA*. 2020.
- 581 3. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for  
582 Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 2016;123(6):1386-  
583 94.
- 584 4. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and  
585 emerging RNA viruses. *Antiviral research*. 2018;153:85-94.
- 586 5. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus  
587 infections. *Pharmacology & therapeutics*. 2020;209:107512.
- 588 6. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nature*  
589 *reviews Drug discovery*. 2020;19(3):149-50.
- 590 7. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA  
591 polymerase. *Proceedings of the Japan Academy Series B, Physical and biological sciences*.  
592 2017;93(7):449-63.
- 593 8. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease  
594 (COVID-19) [Internet]. online: Centre For Disease Control and Prevention; 2020 [updated Dec 8,2020;  
595 cited 2021 18 Jan]. Available from: [https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-  
596 management-patients.html](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).
- 597 9. COVID-19. Coronavirus Disease Guidelines [online]. Kingdom of Saudi Arabia: Ministry of Health;  
598 2020 [cited 2021 18 Jan]. Available from:  
599 <https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx>.
- 600 10. Compendium of Guidelines, Instruction and Standard Operative Procedures for Covid-19  
601 [Internet]. India: Medical Education and Drugs Department Government of Maharashtra; 2020 [cited  
602 2021 18 Jan]. 4:[Available from:  
603 [https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volum  
604 e%204.pdf](https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volume%204.pdf).
- 605 11. Ratanarat R, Sivakorn C, Viarasilpa T, Schultz MJ. Critical Care Management of Patients with  
606 COVID-19: Early Experience in Thailand. *Am J Trop Med Hyg*. 2020;103(1):48-54.
- 607 12. Interim guidelines. Prevention, diagnostics and treatment of a new coronavirus infection  
608 (COVID-19) [Internet]. Russia: MOH of the Russian Federation; 2020 [updated 28 April 2020; cited 2021  
609 18 Jan]. 6:[Available from: [https://static-  
610 1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020\\_%D0%9CR\\_COVID-  
611 19\\_v6.pdf](https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf).

- 1  
2  
3 612 13. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the  
4 613 treatment of COVID-19. *International Journal of Infectious Diseases*. 2021;102:501-8.  
5 614 14. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal*  
6 615 *Medicine*. 2013;158(3):200-7.  
7 616 15. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A  
8 617 Randomized Clinical Trial. medRxiv. 2020:2020.03.17.20037432.  
9 618 16. Favipiravir: Report on the Deliberation Results;. 2014. Japan: Toyama Chemical, Evaluation and  
10 619 Licensing Division PaFSBMoH, Labour and Welfare; 2014 March 4 Report No.  
11 620 17. Heritier SR, GebSKI VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-  
12 621 treat principle. *The Medical journal of Australia*. 2003;179(8):438-40.  
13 622 18. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res*. 2011;2(3):109-12.  
14 623 19. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for  
15 624 COVID-19: An Open-Label Control Study. *Engineering (Beijing, China)*. 2020.  
16 625 20. Kumar A, Chakraborty BS. Interim analysis: A rational approach of decision making in clinical  
17 626 trial. *J Adv Pharm Technol Res*. 2016;7(4):118-22.  
18 627 21. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental  
19 628 Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm  
20 629 Proof-of-Concept Trial in Guinea. *PLoS medicine*. 2016;13(3):e1001967.  
21 630 22. Bai CQ, Mu JS, Kargbo D, Song YB, Niu WK, Nie WM, et al. Clinical and Virological Characteristics  
22 631 of Ebola Virus Disease Patients Treated With Favipiravir (T-705)-Sierra Leone, 2014. *Clinical infectious*  
23 632 *diseases : an official publication of the Infectious Diseases Society of America*. 2016;63(10):1288-94.  
24 633 23. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with  
25 634 Pneumonia in China, 2019. *New England Journal of Medicine*. 2020;382(8):727-33.  
26 635 24. James MI. Preliminary report of favipiravir observational study in Japan released. online: News-  
27 636 Medical.net, 2020.  
28 637 25. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A Prospective,  
29 638 Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with  
30 639 COVID-19. *Antimicrobial Agents and Chemotherapy*. 2020;64(12):e01897-20.  
31 640 26. Singh P. A Clinical Study on Favipiravir Compared to Standard Supportive Care in Patients With  
32 641 Mild to Moderate COVID-19 [Online]. *Cochrane COVID-19 Study Register2020* [updated April ]. Version  
33 642 3 [Available from: ICTRP (<http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43504>)].  
34 643 27. Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered  
35 644 with ClinicalTrials.gov: cross-sectional analysis. *BMJ Open*. 2020;10(9):e041276.  
36 645 28. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical  
37 646 trials assessing treatments for COVID-19: a cross-sectional analysis. *BMJ Open*. 2020;10(6):e039978.  
38 647 29. Listed COVID 19 Studies [Internet]. online: US National Institute of Health (NIH); 2020 [cited 2020  
39 648 26 Nov]. *Clinicaltrials.org*. Available from: <https://www.clinicaltrials.gov>.  
40 649 30. Udhwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and Safety of  
41 650 Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A  
42 651 Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial. *International Journal of*  
43 652 *Infectious Diseases*. 2020.  
44 653 31. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other  
45 654 antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis.  
46 655 *Virology journal*. 2020;17(1):141.  
47 656 32. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best  
48 657 observational study. *BMJ*. 2000;321(7256):255-6.  
49 658 33. Oleckno WA. *Essential Epidemiology: Principles and Applications*. 4180 IL route 83, suite 101  
50 659 Long Grove, IL: Waveland Press, Inc.; 2002.

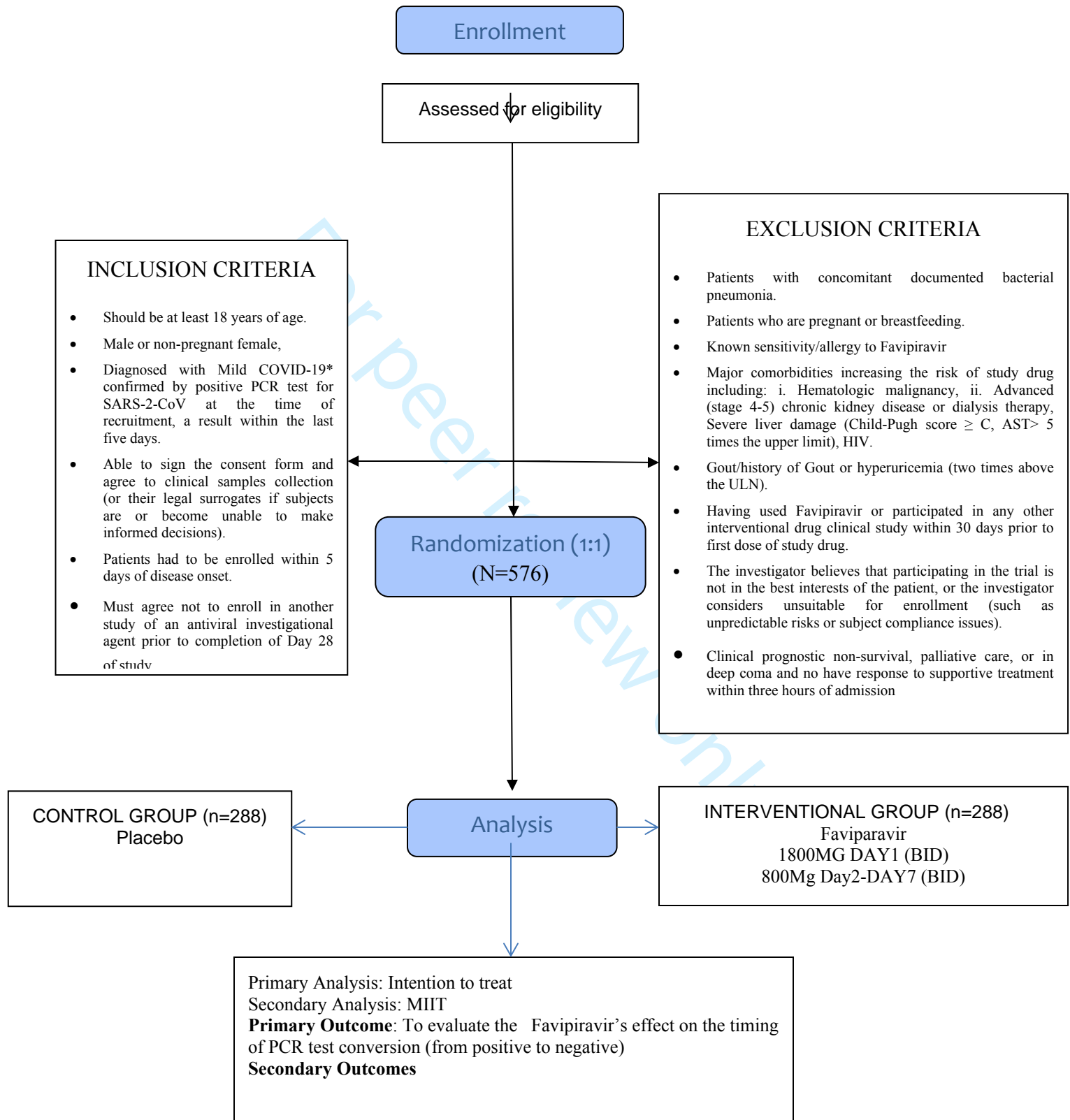
- 1  
2  
3 660 34. Hulley S, Cummings S, Browner W, Grady D, Newman T. Designing clinical research. 503 Walnut  
4 661 street, Philadelphia, PA, USA: Williams and Wilkins .A Walters Kluwer business Lippincot; 2007.  
5 662 35. Manja V, Lakshminrusimha S. Epidemiology and Clinical Research Design, Part 1: Study Types.  
6 663 Neoreviews. 2014;15(12):e558-e69.  
7

8 664  
9  
10  
11  
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13  
14  
15  
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Fig1: AviMild arms. BID, two times per day; MIIT, modified intention to treat

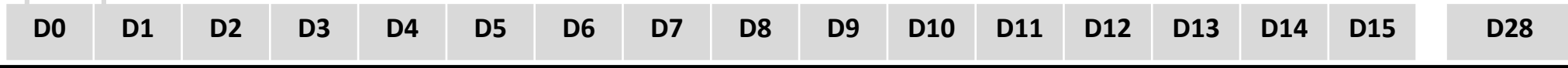


Eligibility assessment  
 Informed consent  
 Randomization  
 Baseline data

Administration of Study Drug:  
 Favipiravir/Placebo  
 Adverse Drug Reactions Assessment

Daily follow-up/ Symptoms Evaluation

Serious Adverse Events Assessment



Medical History

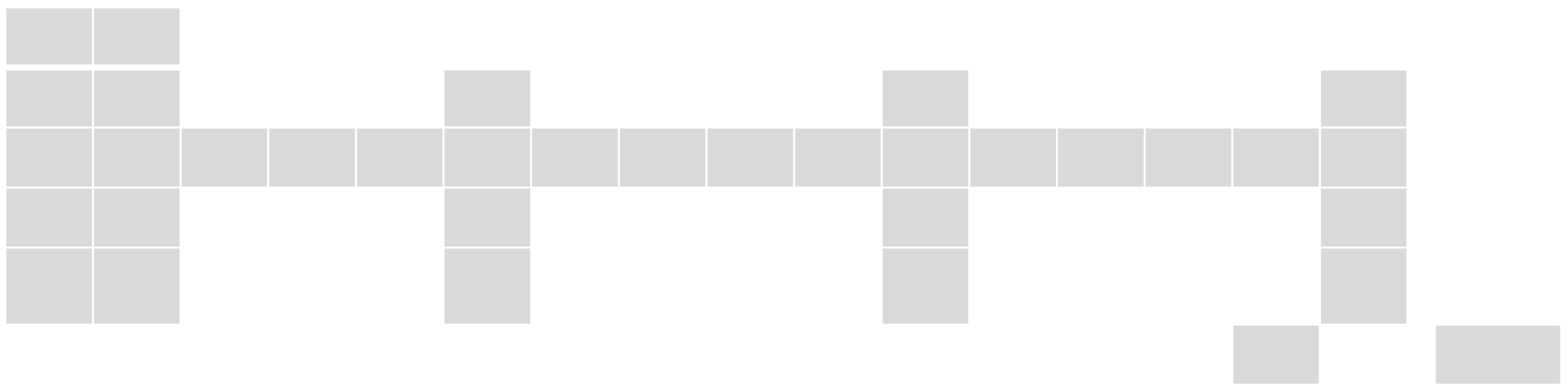
Vital Signs

Clinical Data Collection

SARS-CoV-2 Testing

Blood Tests  
 (CBC, Renal Profile & LFT)

Outcome



# 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  $\geq$  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

1 7.The investigator believes that participating in the  Yes  No  
2 trial is not in the best interests of the patient,  
3 or the investigator considers unsuitable for  
4 enrollment (such as unpredictable risks or subject  
5 compliance issues)

8 8.Clinical prognostic non-survival, palliative care,  Yes  No  
9 or in deep coma and have no response to supportive  
10 treatment within three hours of admission

13 Randomization

16 Site  Site1  
17  Site2  
18  Site3  
19  Site4  
20  Site5  
21  Site6  
22  Site7  
23  Site8  
24  Site9  
25  Site10

27 Patient Recruited in ?  Hospital  
28  Community

30 Treatment  A  
31  B  
32  C  
33  D

35 Randomization Time

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# Co-Morbidities

1  
2  
3  
4  
5 Height6  
7 \_\_\_\_\_  
(cm)8  
9 Weight10  
11 \_\_\_\_\_  
(kg)**Co-morbidities and risk factors - Charlson Index will be calculated for each patient at analysis.**

	Yes	No	NA
17 Hypertension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18 Chronic cardiac disease, 19 including congenital heart 20 disease (not hypertension)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
23 Chronic pulmonary disease (not 24 asthma)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25 Asthma (physician diagnosed)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
27 Chronic kidney disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
28 Chronic liver disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 Chronic neurological disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
31 Chronic 32 Rheumatologic/Auto-immune 33 disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
35 Obesity (BMI more than 30)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
36 Diabetes with complications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
37 Diabetes without complications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
39 Smoking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
40 Other	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

41  
42  
43 Specify, Other Co-Morbidities44  
45 \_\_\_\_\_  
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# 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
8 Fever	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9 Cough	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10 Cough with Sputum Production	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11 Cough with Bloody Sputum/Haemoptysis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12 Sore Throat	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13 Runny Nose (Rhinorrhoea)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14 Chest Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15 Shortness of Breath (Dyspnea)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16 Loss of smell	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17 Loss of taste	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18 Abdominal Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19 Vomiting / Nausea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20 Diarrhoea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21 Ear Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22 Muscle Aches (Myalgia)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
23 Joint Pain (Arthralgia)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24 Fatigue / Malaise	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25 Lower Chest Wall Indrawing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
26 Headache	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
27 Conjunctivitis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
28 Skin Rash	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
29 Skin Ulcers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 Lymphadenopathy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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# Daily Clinical Assessment

**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)

1 Systolic Blood Pressure \_\_\_\_\_  
2  
3 (mmHg)

5 Diastolic Blood Pressure \_\_\_\_\_  
6  
7 (mmHg )

10 Mean Arterial Blood Pressure \_\_\_\_\_  
11  
12 (mmHg )

14 Urine flow rate \_\_\_\_\_  
15  
16 (mL/24 hours Check if estimated )

18 Glasgow Coma Score (GCS / 15) \_\_\_\_\_  
19  
20

**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
26 Non-invasive ventilation (e.g. BIPAP, CPAP)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
29 Invasive ventilation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 Extra corporeal life support (ECLS)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
32 High-flow nasal cannula oxygen therapy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
34 Dialysis/Hemofiltration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
36 Any vasopressor/inotropic support	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

38 Progress of Symptoms at 1st Presentation(pyrexia, short of breath, and relief of cough and/or others)  
39 Can stop recording if resolved for 72 hours  
40  
41  Worsening  
42  Same  
43  Better  
44  Resolved

**Signs and Symptoms**

46 New signs and symptoms  Yes  No

49 Specify, \_\_\_\_\_  
50  
51 (L/min)

53 Starting Date \_\_\_\_\_  
54  
55

57 Fever  Yes,  No

1 Fever Result

2  
3 \_\_\_\_\_  
4 (°C)

5 Any hospital/ER visits

6  Yes  No

7  
8  
9 Was Vital Signs Collected?

10  Yes  No

11  
12  
13  
14 Temperature

15 \_\_\_\_\_  
16 (°C)

17  
18 Heart Rate

19 \_\_\_\_\_  
20 ( Beat Per Minut)

21  
22  
23 Respiratory Rate

24 \_\_\_\_\_  
25 (Breath Per Minute)

26  
27  
28 Systolic Blood Pressure

29 \_\_\_\_\_  
30 (mmHg)

31  
32 Diastolic Blood Pressure

33 \_\_\_\_\_  
34 (mmHg)

35  
36 Oxygen Saturation

37 \_\_\_\_\_  
38 (%)

39  
40  
41 Oxygen On

42  Room air  Oxygen therapy  
43  NA

44 Specify, Oxygen Therapy

45 \_\_\_\_\_  
46  
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# 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

For peer review only

# 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 ( $\pm 1$  day)  
 Day 10 ( $\pm 1$  day)  
 Day 15 ( $\pm 2$  day)

## Laboratory Assessment

Haemoglobin

\_\_\_\_\_

- g/L    g/dL

WBC Count

\_\_\_\_\_

- $\times 10^9/L$      $\times 10^3/\mu L$

Lymphocyte count

\_\_\_\_\_

(cells/  $\mu L$ )

Neutrophil count

\_\_\_\_\_

(cells/  $\mu L$ )

Platelets

\_\_\_\_\_

- $\times 10^9/L$      $\times 10^3/\mu L$

ALT/SGPT

\_\_\_\_\_

(U/L)

Total Bilirubin

\_\_\_\_\_

- $\mu mol/L$     mg/dL

AST/SGOT

\_\_\_\_\_

(U/L)

Glucose

\_\_\_\_\_

1 \_\_\_\_\_  mmol/L  mg/dL

2

3

4 Blood Urea Nitrogen (urea)

5 \_\_\_\_\_

6

7 \_\_\_\_\_  mmol/L  mg/dL

8

9 \_\_\_\_\_  mmol/L  mg/dL

10

11 Creatinine

12 \_\_\_\_\_

13

14 \_\_\_\_\_  umol/L  mg/dL

15

16

17 Sodium

18 \_\_\_\_\_

19 (mEq/L)

20

21 Potassium

22 \_\_\_\_\_

23 (mEq/L)

24

25

26 Chest X-Ray performed?  Yes  No  NA

27

28

29 Were Infiltrates Present?  Yes-Unilateral  Yes - Bilateral

30  No  NA

31

32

33

34

35

36 ECG performed?  Yes

37  No

38  N/A

39 if YES QT Interval

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# Daily Study Drug

## Favipiravir / Placebo

Was Favipiravir given?

- Yes
- No

Dose

\_\_\_\_\_

Dose Number

\_\_\_\_\_

Date

\_\_\_\_\_

Time given

\_\_\_\_\_

Drug Method

- Syrup
- tablet

For peer review only



# 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	<input type="radio"/>	<input type="radio"/>
Bacterial Pneumonia	<input type="radio"/>	<input type="radio"/>
Coagulopathy	<input type="radio"/>	<input type="radio"/>
Acute lung Injury/ARDS	<input type="radio"/>	<input type="radio"/>
Anemia	<input type="radio"/>	<input type="radio"/>
Pneumothorax	<input type="radio"/>	<input type="radio"/>
Pleural Effusion	<input type="radio"/>	<input type="radio"/>
Acute renal Injury/Failure	<input type="radio"/>	<input type="radio"/>
Seizure	<input type="radio"/>	<input type="radio"/>
Congestive Heart Failure	<input type="radio"/>	<input type="radio"/>
Meningitis/ Encephalitis	<input type="radio"/>	<input type="radio"/>
Stroke/Cerebrovascular Accident	<input type="radio"/>	<input type="radio"/>
Endocarditis / Myocarditis / Pericarditis	<input type="radio"/>	<input type="radio"/>
Cardiac Arrhythmia	<input type="radio"/>	<input type="radio"/>
Bacteremia	<input type="radio"/>	<input type="radio"/>
Cardiac Arrest	<input type="radio"/>	<input type="radio"/>
Liver Dysfunction	<input type="radio"/>	<input type="radio"/>
Rhabdomyolysis / Myositis	<input type="radio"/>	<input type="radio"/>
Other	<input type="radio"/>	<input type="radio"/>

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

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Last/End Date

OTHER Intervention or Procedure

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# 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

\_\_\_\_\_

1 Azithromycin\_end date \_\_\_\_\_  
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5 Interferon Dose \_\_\_\_\_  
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8 Interferon\_Start date \_\_\_\_\_  
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10 \_\_\_\_\_  
11 Interferon\_End date \_\_\_\_\_  
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13 \_\_\_\_\_  
14 Oseltamivir Dose \_\_\_\_\_  
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16 \_\_\_\_\_  
17  
18 Oseltamivir\_Start date \_\_\_\_\_  
19  
20 \_\_\_\_\_  
21 Oseltamivir\_End date \_\_\_\_\_  
22  
23 \_\_\_\_\_  
24 Anti-Interleukin-6 Agents?  Yes  No  
25  
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28 Please ,Provide Type \_\_\_\_\_  
29  
30 \_\_\_\_\_  
31 Please ,Provide the Dose \_\_\_\_\_  
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33 \_\_\_\_\_  
34 Antibiotic?  Yes  No  NA  
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36  
37  
38 Dose \_\_\_\_\_  
39  
40 \_\_\_\_\_  
41 Type \_\_\_\_\_  
42  
43 \_\_\_\_\_  
44 Is the patient take another antibiotic?  Yes  No  NA  
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48 Antibiotic\_2 Type \_\_\_\_\_  
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52 Antibiotic\_2 Dose \_\_\_\_\_  
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54 \_\_\_\_\_  
55 Antibiotic\_3 Type \_\_\_\_\_  
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58 Antibiotic\_3 Dose \_\_\_\_\_  
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1 Antibiotic\_4 Type \_\_\_\_\_  
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3 \_\_\_\_\_  
4  
5 Antibiotic\_4 Dose \_\_\_\_\_  
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7 \_\_\_\_\_  
8 Convalescent plasma?  Yes  No  N/A  
9  
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11 Specify \_\_\_\_\_  
12  
13 \_\_\_\_\_  
14 Corticosteriod?  Yes  
15  No  
16  
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19 Dose \_\_\_\_\_  
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21 \_\_\_\_\_  
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23 Type \_\_\_\_\_  
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25 \_\_\_\_\_  
26 Duration \_\_\_\_\_  
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For peer review only

# Outcome

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## 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

\_\_\_\_\_

FO peer review only



# 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

1 OtherI  No  1  2  3  
 2  4  5

4 Specify, \_\_\_\_\_  
 5  
 6

8 OtherII  No  1  2  3  
 9  4  5

11 Specify, \_\_\_\_\_  
 12  
 13

15 **Central Nervous System**

17 Headache  No  1  2  3

20 Insomnia  No  1  2  3

23 Psychosis  No  1  2  3  
 24  4  5

27 Depression  No  1  2  3  
 28  4  5

30 Mania  No  1  2  3  
 31  4  5

33 ECG: QT Interval Changes  No  1  2  3  
 34  4  5

37 OtherI  No  1  2  3  
 38  4  5

40 Specify, \_\_\_\_\_  
 41  
 42

43 OtherII  No  1  2  3  
 44  4  5

46 Specify, \_\_\_\_\_  
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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 1<sup>st</sup> 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

1 suspected pregnant females in this study.  
2  
3

#### 4 **9. Costs and compensation for participation in this study:**

5  
6 You will not receive any compensation for your participation in this trial. However, in the event of  
7 an illness or injury related to the study medication, all treating procedures, follow-ups,  
8 hospitalization, will be provided to you immediately.  
9

#### 10 **10. Benefits:**

11  
12 Previous studies done in USA and JAPAN have shown that this medication had a positive effect in  
13 treating influenza virus.  
14

15  
16 You may or may not benefit directly from participating in this research, but your participation may  
17 help other patients with COVID-19.  
18

19  
20 This research study will increase the medical knowledge which will help to decide if  
21 FAVAPIRAVIR medication can be used in treatment of COVID-19 in the future.  
22  
23

#### 24 **11. Alternative Treatment(s):**

25  
26 You will be receiving the routine treatment as per the treating physicians during the course of the  
27 study and you will be made aware of any new treatment available for the disease.  
28  
29

#### 30 **12. Information about participation:**

31  
32 Your participation in this study is totally voluntary, you have the right to withdraw at any time you  
33 want without mentioning the reasons. If you do not want to take part, you will receive standard care  
34 provided by your doctor, and your decision about the study will not affect your current or future  
35 medical care.  
36  
37

38 The study doctor and the study sponsor have the right to withdraw you from the study if he decided  
39 that it's better for your medical condition. Or you did not comply with study requirements.  
40

41 If you have any other diseases or adverse events the principal investigator will decide whether to  
42 continue with participation in the study or not.  
43  
44

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

46  
47 All information related to you including personal and medical data provided and collected by the  
48 study doctor and recorded in the study records will be handled as confidential and no one except  
49 authorized research team at King Abdullah International Medical Research Center (KAIMRC),  
50 Sponsors, Institutional Review Board (IRB), Research Scientific Committee (RC), Ministry of  
51 Health auditors, the Saudi Food and Drug Administration (SFDA) and related personnel that can  
52 have access to record, review and analyze them.  
53

54  
55 All the information collected in subjects records belong to King Abdullah International Medical  
56 Research Center. In case any results of the study are published, your personal information will never  
57 be mentioned, it may be coded in symbols known for research team  
58  
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#### 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.

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



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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



1	<b>Introduction</b>			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	4
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	4
7				
8	Objectives	7	Specific objectives or hypotheses	10
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	6
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	8
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	11
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	9
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
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34	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	
35			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	10
36			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
37			efficacy and harm outcomes is strongly recommended	
38				
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40	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	8
41			participants. A schematic diagram is highly recommended (see Figure)	
42				
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1	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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
5				

## 6 **Methods: Assignment of interventions (for controlled trials)**

### 7 Allocation:

8				
9				
10	Sequence	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
11	generation			
12				
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16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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## 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	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
34	methods			
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39		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
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1	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
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5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
9				
10		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
11				
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14	<b>Methods: Monitoring</b>			
15				
16	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
17				
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22		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
23				
24				
25	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
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
29				
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
35				
36				
37	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
38				
39				
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46				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
11				
12				
13	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
14				
15				
16	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
17				
18				
19				
20	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
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
32				
33				
34	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
35				
36				

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# BMJ Open

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

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

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53  
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59

## 60 **ABSTRACT**

### 61 **Introduction**

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

### 67 **Methods and Analysis**

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

72 Adults (>18 years, male or non-pregnant female, diagnosed with mild COVID-19 within five  
73 days of disease onset) are being recruited by physicians participating from the Ministry of  
74 National Guard Health Affairs(MNGHA) and Ministry of Health(MOH) ethics committee  
75 approved primary health care centers. This double-blind, randomized trial comprises three  
76 significant parts screening, treatment, and follow-up period, where treating physician and  
77 patients are blinded. Eligible participants will be randomized in a 1:1 ratio to either the therapy  
78 group (Favipiravir) or a control group (Placebo) with 1800 mg by mouth twice daily for the first  
79 day, followed by 800mg twice daily for 4-7 days. Serial nasopharyngeal/Oropharyngeal swab  
80 samples will be obtained on day 1(-5 days before therapy). On day's 5±1 day, 10±1day,  
81 15±2days, extra nasopharyngeal/ Oropharyngeal PCR COVID-19 samples will be requested.

1  
2  
3 82 The primary analysis population for evaluating both efficacy and safety outcomes will be a  
4 83 modified ITT population. Anticipating a 10% drop-out rate, we expect to recruit 288 subjects per  
5 84 arm. The results assume that the hazard ratio is constant throughout the study and that Cox  
6 85 proportional hazards regression is used to analyze the data.

### 10 86 **Ethics and dissemination**

11 87 The study was approved by the King Abdullah Medical Research Centre Institutional Review  
12 88 Board (28 April 2020) and the Ministry of Health Institutional Review Board (1 July 2020).  
13 89 Protocol details and any amendments will be reported  
14 90 to <https://clinicaltrials.gov/ct2/show/NCT04464408>. Results will be published in peer-reviewed  
15 91 journals.

16 92 **Trial registration number:** National Clinical Trial Registry (NCT04464408)  
17 93  
18 94  
19 95

### 26 96 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 27 97 ➤ Double blind randomized placebo controlled trial.
  - 28 98 ➤ Large sample size of 576 participants.
  - 29 99 ➤ Recruiting is challenging as subjects need to be enrolled within 5 days of disease onset.
  - 30 100 ➤ Challenging remote site initiation visit, protocol training and monitoring activities.
  - 31 101 ➤ Staff shortage for research due to allocation to other clinical services to address the  
32 102 burden of the pandemic
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113

## 114 INTRODUCTION

115 In December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international  
116 outbreak of respiratory illness termed COVID-19. The WHO declared the epidemic of COVID-  
117 19 as a pandemic on 12th March 2020. (1) According to a recent Chinese study, “about 80% of  
118 patients present with mild disease, and the overall case-fatality rate is about 2.3% but reaches  
119 8.0% in patients aged 70 to 79 years”. (2) Mild cases have been found to have viral loads 60-fold  
120 less than severe cases. The viral loads of asymptomatic individuals are lower, with possible  
121 implications for infectiousness and diagnosis.(2) In Saudi Arabia, as of 25th Feb 202, 376,000  
122 confirmed cases of the disease were reported.(3) There are no specific therapeutic agents based  
123 on substantial evidence for these novel coronavirus infections; however, several medications  
124 have been evaluated as a potential therapy. Therapy is warranted to treat symptomatic patients  
125 and decrease virus carriage duration to limit the community’s transmission.

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

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

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

1  
2  
3 143 mild to moderate COVID-19 in the treatment guidelines. (8-13) Thus, we want to prove the  
4  
5 144 effectiveness of this therapy in treating mild COVID-19 cases.  
6

### 7 145 **Research Hypothesis**

8  
9 146 We hypothesize that mild COVID-19 patients treated with Favipiravir will have a shorter  
10  
11 147 duration of time to virus clearance than the control group.  
12

## 13 148 **METHODS AND ANALYSIS**

### 14 149 **Study Design**

15  
16 150 AviMild is a phase III randomized double-blinded placebo-controlled parallel-group multicenter  
17  
18 151 clinical trial to evaluate Favipiravir's safety and efficacy in adults diagnosed with mild COVID-  
19  
20 152 19. The trial involves patients from the community settings from different cities in Saudi Arabia  
21  
22 153 with King Abdullah International Medical Research Center (KAIMRC) as the sponsor. The  
23  
24 154 protocol described in this article is V2.2 approved on 20 Nov 2020. This RCT has been  
25  
26 155 developed according to the Standard Protocol Items: Recommendations for Intervention Trials  
27  
28 156 2013 statement. (14)

29  
30 157 AviMild RCT will compare Favipiravir (experimental arm) to a control arm (Placebo). Patients  
31  
32 158 will be randomly assigned in a 1:1 ratio to both arms. Figure 1 provides an overview of the study  
33  
34 159 design. Any investigational antiviral medication for COVID-19 and other types of antiviral drugs  
35  
36 160 are prohibited. Patients are allowed to continue the medications they were taking before the  
37  
38 161 study, e.g., anti-hypertensive or antidiabetics. The patients are not allowed to participate in other  
39  
40 162 trials as per the study protocol. This is a double-blind study where the treating physician and  
41  
42 163 patients are blinded. The study's recruitment start date was 23 July 2020, and it will continue till  
43  
44 164 reaching the sample size or up to Dec 2021. The trial is registered at the ClinicalTrials.org  
45  
46 165 registry as NCT04464408.  
47

### 48 166 **Study Population**

49 167 A convenience sample of adult patients with mild COVID-19 infection identified as positive by  
50  
51 168 PCR confirmed SARS-CoV -2 from the community. Patients eligible at the Ministry National  
52  
53 169 Guard Health Affairs (MNGHA) at Riyadh and Madinah, Saudi Arabia, will be assessed for  
54  
55 170 inclusion in the trial. Additionally, positive patients visiting the Ministry of Health (MOH)  
56  
57 171 Institutional Review Board (IRB) and Saudi Food Drug Authority (SFDA) approved primary  
58  
59 172 health care centers in the regions of Riyadh, Makkah and Madinah will also be assessed for  
60  
173 eligibility. Presently there are seven centers, including the sponsor site. Ministry National Guard

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2  
3 174 Health Affairs (MNGHA) Riyadh, Primary Health Care (PHC)- Mansoura and PHC-Al Urijah  
4  
5 175 Riyadh, MNGHA Madinah and PHC Safiyah -Madinah, King Fahad Hospital -Madinah, King  
6  
7 176 Abdullah Medical City- Makkah..

8 177 The sponsor has subscribed an insurance policy covering the sponsor's own third-party liability  
9  
10 178 as well as the third-party liability of all the investigators involved for the study's duration.  
11

12 179

### 13 180 **Inclusion Criteria**

14 181 Patients must be eligible according to the following criteria for enrollment

15 182

16 183 (1) Should be at least 18 years of age

17  
18 184 (2) Male or non-pregnant female (pregnancy testing is not mandatory. If the patient requests or is  
19  
20 185 not sure, the study team will provide it)

21 186 (3) Diagnosed with mild COVID-19\* confirmed by positive PCR test for SARS-CoV-2 at the  
22  
23 187 time of recruitment, a result within the last five days

24  
25 188 (4) Patients have to be enrolled within 5 days of disease onset.

### 26 189 **Exclusion criteria**

27  
28 190 Patients meeting any of the following criteria will be excluded from trial enrolment:

29  
30 191 (1) Patients with concomitant documented bacterial pneumonia established through positive  
31  
32 192 sputum cultures

33 193 (2) Patients who are pregnant or breastfeeding

34  
35 194 (3) Known sensitivity/allergy to Favipiravir (If Favipiravir was used for COVID-19 in the  
36  
37 195 patient previously for influenza)

38  
39 196 (4) Major comorbidities increasing the risk of study drug including

40  
41 197 

- Hematologic malignancy

42 198 

- Advanced (stage 4-5) chronic kidney disease or dialysis therapy

43  
44 199 

- Severe liver damage (Child-Pugh score C, AST> 5 times the upper limit)

45  
46 200 

- HIV

47  
48 201 

- Gout/history of Gout or hyperuricemia (two times above the ULN)

49 202 (6) Having used Favipiravir or participated in any other interventional drug clinical study within  
50  
51 203 30 days before the first dose of study drug (i.e., the patient received it for influenza previously)

52  
53 204 (7) The investigator believes that participating in the trial is not in the best interests of the  
54  
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3 205 patient, or the investigator considers unsuitable for enrollment (such as unpredictable risks or  
4 206 subject compliance issues)

5  
6 207 (8) Clinical prognostic non-survival, palliative care, or in a deep coma and have no response to  
7 208 supportive treatment within three hours of admission.

8  
9  
10 209 (9) Hospitalized patients for moderate or severe COVID-19

11  
12 210 Definitions:

13 211 a. Mild COVID-19 cases are defined as a patient presenting with a mild illness (absent or mild  
14 212 pneumonia), oxygen saturation >94% at room air, and not requiring ICU admission.

15 213 Mild illness may include uncomplicated upper respiratory tract viral infection symptoms such as  
16 214 fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore  
17 215 throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea,  
18 216 nausea, and vomiting.

19 217 b. Viral clearance is defined as polymerase chain reaction (PCR) negative results.

## 20 218 **Randomization**

21 219 Eligible participants will be randomized in a 1:1 ratio to either the therapy group (Favipiravir) or  
22 220 a control group (placebo). The randomization list is computer generated and is stratified by  
23 221 clinical site. The patients will be randomized, utilizing an electronic case report (e-CRF) form  
24 222 (REDCAP) to ensure allocation concealment. The sequence of treatment assignments will be  
25 223 determined before the start of the study.

## 26 224 **Blinding**

27 225 The trial is double-blind, meaning that the participants, investigators, and other study staff are  
28 226 unaware of the treatment assignment. The Sponsor's investigational drug unit, not part of the  
29 227 study team holds the information for treatment allocation.

## 30 228 **RATIONALE FOR STUDY TREATMENT**

31 229 Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase. It acts as a  
32 230 purine analog, which selectively inhibits viral RNA-dependent RNA polymerase (RdRps).

33 231 Favipiravir has the characteristic of acting on RNA viruses, including Ebola and Coronaviruses  
34 232 especially, novel coronavirus. For the Ebola virus, favipiravir effectively prevented Ebola in  
35 233 mice by 100%, although EC50 (drug concentration was found to reduce viral replication by  
36 234 50%) ~67 µM. A recent in vitro study on clinical isolates of COVID-19 showed that Favipiravir  
37 235 has EC50 =61.88µM. (15) ). The dose was chosen based on the drug insert (Fabiflu Prescribing

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

238

239

#### 240 **Participant Timeline**

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

#### 251 Screening/Baseline: Day -1 to Day1

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

#### 261 Treatment Period: DAY 1

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

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

268 Treatment compliance

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

273 Follow-up Period-Day1-15 and Day 28

274 The follow-up period starts from the second day after randomization for 14 days, where the  
275 research coordinator or the physician will follow-up the patient's health through a phone call.  
276 Follow-up of symptoms evaluation should be for 15 days or until the patient reaches the  
277 secondary endpoint (resolving symptoms). The patient's assessment will be recorded in the e-  
278 CRF. Another follow-up will be made on day 28 days from randomization. On day's 5±1 day,  
279 10±1day, 15±2days, extra nasopharyngeal/ oropharyngeal PCR COVID-19 samples will be  
280 requested by delegated specialist trained clinical personnel part of the research team, and results  
281 documented in e-CRF. Patients' follow-up and needed laboratory investigations will be done  
282 while the patient is in the hospital. If the patient is discharged or in outpatient settings, the  
283 follow-up evaluation and obtaining specimens will be done by delegated personnel in the  
284 outpatient clinic or mobile team trained as per study protocol.

285 **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.

288

## 289 OUTCOME MEASUREMENTS

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

### 293 Primary outcome

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

### 296 Secondary Outcome

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

- 1  
2  
3 307 ➤ Evaluate the safety of investigational drug compared to the control arm within 15 days after  
4 308 starting the medicine. This is assessed by allergic reactions, medication intolerance, liver  
5 309 toxicity, and hyperuricemia in subjects.  
6  
7  
8 310

## 9 311 **PARTICIPANT DISCONTINUATION**

11 312 Premature discontinuation of the trial would be based on the decision of the Data Safety  
12 313 Monitoring Board (DSMB), or the investigator-initiated based on the following:

- 15 314 1. Adverse event: clinical or laboratory event, that in the medical judgment of the  
16 315 investigator, for the best interest of the patient are grounds for discontinuation  
18 316 2. A major deviation from the protocol: the patient's findings or conduct failed to adhere to  
19 317 the protocol requirements.

22 318 Other reasons: e.g., an administrative problem such as termination of study by the sponsor.

## 25 319 **DATA COLLECTION, MANAGEMENT AND ANALYSIS**

26 320  
27 321 The research coordinator with expertise in data entry will enter data into a password-protected  
28 322 database (REDCAP). All observations and other data pertinent to the clinical investigation will  
29 323 be recorded into the e-CRF. Data will be entered and double-checked for accuracy. After  
30 324 resolving any discrepancies and a combination of manual and automated data-review procedures,  
31 325 the final data set will be subject to a quality assurance audit.

36 326 A clinical data management review will be performed on all subject data to ensure clinical data  
37 327 quality across all participants and sites. During this review, subject data will be checked for  
38 328 consistency, omissions, and any apparent discrepancies. Also, the data will be reviewed for  
39 329 adherence to the protocol. During data analysis, non-identifiable data will be provided in a  
40 330 password protected excel sheet. All data are de-identified and coded with a unique number  
41 331 generated by the online data management system REDCAP.

## 48 332 **SAFETY AND ADVERSE EVENTS MONITORING**

49 333 All adverse events (AE) and serious adverse event (SAE) encountered during the clinical study  
50 334 will be reported on the e-CRF. The information to be entered in the e-CRF will include:

- 53 335 • The time of onset of any AE or the worsening of a previously observed AE  
54 336 • The specific type of reaction in standard medical terminology

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3 337 • The duration of the AE (start and stop dates)  
4  
5 338 • The severity of the adverse event (AE). The severity should be rated as:  
6  
7 339 ○ Mild: discomfort noted, but no disruption of normal daily activity.  
8  
9 340 ○ Moderate: discomfort noted of sufficient severity to reduce or adversely affect  
10 normal activity.  
11 341  
12 ○ Severe: incapacitating, with the inability to work or perform normal daily activity.  
13 342  
14  
15 343 • The assessment of the relationship of adverse event (AE) to study medication, i.e.,  
16 according to the definitions below:  
17 344  
18 ○ Related: with a reasonable causal relationship to the investigational product.  
19 345  
20 ○ Not Related: without a reasonable causal relationship to the investigational  
21 346 product.  
22 347  
23 ○ Other: in such a case, the investigator's causality assessment should be specified.  
24 348  
25  
26 349 • Description of action taken in treating the AE and/or change in study medication  
27 administration or dose.  
28 350  
29  
30

31 351 As far as possible, all investigators will follow-up participants with AEs until the event is  
32 352 resolved or until, in the investigator's opinion, the event is stabilized or determined to be chronic.  
33 353 Details of AE resolution will be documented in the e-CRF. Any significant changes in AEs will  
34 354 be reported even though the subject has completed the study, including the protocol-required  
35 355 post-treatment follow-up.  
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## 40 356 **STATISTICAL METHODS**

### 41 357 **General Considerations**

42 358 This is a randomized, double-blinded study comparing Favipiravir tablets to placebo group to  
43 359 treat subjects with mild SARS-CoV-2 infection. The Intention to treat (ITT) analysis will include  
44 360 all subjects randomized which will ignore noncompliance, protocol deviations, withdrawal, and  
45 361 anything that will take place after randomization. (17, 18) The primary analysis population for  
46 362 evaluating both efficacy and safety outcomes will be a modified ITT population, and will include  
47 363 all subjects who have been randomized but will exclude some randomized subjects like patients  
48 364 who were judged ineligible after randomization or patients who withdrew consent or certain  
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3 365 patients who never started treatment (17, 18), study drug (Favipiravir tablets or Placebo) was  
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5 366 started, and the patient did not withdraw consent. These results assume that the hazard ratio is  
6  
7 367 constant throughout the study and that Cox proportional hazards regression is used to analyze the  
8  
9 368 data.

## 10 369 **Sample Size and Power Considerations**

### 11 370 Assumptions and Study Hypothesis

- 14 371       a. The current study's primary hypothesis is  $H_0: HR = 1$  vs.  $H_1: HR \neq 1$ ; and HR is  
15  
16 372 the hazard ratio of treatment compared to control arm.
- 17 373       b. Time to viral clearance  
18  
19 374       In patients with mild COVID-19, 90% of the patients clear the virus by day 10 of  
20  
21 375 onset.(1) If we assume an exponential hazard, we estimate the median time of  
22  
23 376 viral clearance in the placebo group to be 8 days.
- 24 377       c. The exact treatment effect from Favipiravir is not known but can be approximated  
25  
26 378 using prior clinical studies. A study comparing Favipiravir's effect to  
27  
28 379 lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral  
29  
30 380 clearance in the Favipiravir arm.(19) To stay on the conservative side, we assume  
31  
32 381 that Favipiravir will reduce the median time to virus clearance to 6 days which is  
33  
34 382 equivalent to hazard ratio of 1.33.
- 35 383       d. We further assume that 90% of the control group patients will have viral  
36  
37 384 clearance within 15 days, and 90% will have viral clearance in the treatment arm.  
38  
39 385 It is anticipated that very few of these subjects will be randomized and not start  
40  
41 386 study treatment (and so be excluded from the primary analysis) or be lost to  
42  
43 387 follow-up (and so have missing data for the primary endpoint). Given certain  
44  
45 388 uncertainties however, we have included a nominal 10% drop out rate.

### 46 389 *Sample Size Estimation for Classical Two Arm Parallel Design*

47  
48 390 Under the classical two-arm parallel design, a one-sided test of whether the hazard ratio is 1 with  
49  
50 391 an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the  
51  
52 392 treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is  
53  
54 393 1.330.

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3 394 The sample size re-estimation will be based on the ratio of the planned effect size (1.33) to the  
4  
5 395 observed effect size from the interim analysis according to the following formula:

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

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8 396  
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10  
11 397 where ‘a’ is a constant which will be set to 2 and is a number chosen to be slightly larger than the  
12  
13 398 classical sample size per group, is the planned effect size of 1.33, and E is the observed effect  
14  
15 399 size from the interim analysis.

16 400 A detailed statistical analysis plan will be developed before undertaking any comparative  
17  
18 401 analyses of outcomes. The following provides a summary of the approach to analysis for the  
19  
20 402 primary endpoint.

21  
22 403 *Analysis of the primary endpoint:*

23 404 The primary endpoint of the current study is the rate of viral clearance. The number and percent  
24  
25 405 of subjects who met the endpoint by day 15 of follow up will be calculated and tabulated. Due to  
26  
27 406 the nature of the data collection (i.e., subjects clearance will be observed during specific follow-  
28  
29 407 up time), survival analysis methods for interval-censored data will be used to analyze the data.  
30  
31 408 All results will be reported in H.R and the corresponding lower confidence limit and one-sided p-  
32  
33 409 value.

34 410 *Analysis for secondary endpoints:*

- 35  
36 411
- 37 • Quantitative variables such as ‘change from baseline in clinical scores’ are expected to  
38 have reasonably skewed distributions. They may be subject to censoring, e.g., for  
39 subjects in hospital on day 28, compared between randomized arms using non-parametric  
40 tests (Wilcoxon’s test).  
41  
42
  - 43 • Analysis of the other secondary endpoints will use a proportional odds model with an  
44 indicator variable for randomized treatment. The Wald test will generate a p-value  
45 comparing treatments and the estimated proportional odds ratio comparing treatments  
46 with associated 95% CI.  
47  
48
  - 49 • Analysis of AE data will primarily be descriptive based on MedDRA coding of events.  
50 The proportion of subjects experiencing an SAE and the proportion experiencing a  
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60 421 Grade

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3 422 • Three or higher AEs will be compared between randomized arms using Fisher's Exact  
4 423 Test.

5 424  
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7 424  
8 425 For enrolled subjects who were not randomized (i.e., screen failures) or randomized but did not  
9 426 receive the treatment, the final analysis will detail safety (deaths and SAEs) and reasons they  
10 427 were not randomized or did not receive treatment, respectively.

11  
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13  
14 428 **DATA MONITORING:**

15 429 This committee will be independent of the sponsor with relevant therapeutic and biostatistical  
16 430 experience to allow for the ongoing review of data from this trial. A Data and Safety  
17 431 Management Board (DSMB) will be convened to monitor the trial's unblinded data focusing  
18 432 mainly on assuring that the study follows the protocol correctly and monitoring the safety issues  
19 433 related to the trial. The DSMB will meet when AEs trigger study pausing/stopping criteria are  
20 434 triggered. The DSMB has no competing interests.

21 435 The current study will have a single interim analysis, which will occur after the recruitment and  
22 436 follow-up of 40% of the total number of subjects (i.e., 230 subjects). The interim analysis is  
23 437 designed to test for early stopping for futility or efficacy and sample size re-estimation.(20) The  
24 438 interim analysis and final analysis will be based on the sum of the stage-wise p-value. Table 2  
25 439 describes the interim analysis testing boundaries.

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35 440 **Table 2: Interim analysis and sample size Re-estimation**

36 37 38 39 40 41 42 43 44 45 46 47 48 49	Alpha1 = 0.01	Stop the trial for early efficacy if the interim analysis p-value is less than 0.01
50 51 52 53 54 55 56 57 58 59 60	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

441

442 Frequency and procedures for auditing trial conduct:

1  
2  
3 443 The investigator will allow representatives of the regulatory authorities (Saudi Food & Drugs  
4 Authority) to conduct an audit anytime they request it. The regulatory authorities are independent  
5 444  
6 445 from the sponsor.  
7  
8 446

## 10 447 **DISCUSSION**

11 448 During the Ebola virus disease outbreak, the JIKI trial illustrated an improved survival rate in  
12 449 patients with moderate to high viral load with favipiravir. (21) Similarly, Bai et al.'s study  
13 450 proved a significant decline in viral load with favipiravir in patients with moderate viral load at  
14 451 baseline. (22) These findings support the role of favipiravir in viral load reduction. Since the  
15 452 homology of gene sequences of SARS-CoV-2 and SARS was over 90%, it is expected that the  
16 453 intervention of antiviral drugs in COVID-19 patients will likely improve or shorten the time to  
17 454 viral clearance. (23) The reduction in time to viral clearance is chosen as the endpoint based on  
18 455 the above evidence. Therefore, viral clearance, which captures the viral shedding duration and  
19 456 possible contagiousness period, reflects the best assessment. Several published trials have  
20 457 studied similar endpoints as our study due to their clinical significance. A study of 80 patients  
21 458 with COVID-19 compared Favipiravir to lopinavir/ritonavir. The study reported a shorter viral  
22 459 clearance time for the Favipiravir arm versus the lopinavir/ritonavir arm median 4 days (IQR:  
23 460 2.5–9) versus 11days (IQR: 8–13),  $P < 0.001$ . Multivariable Cox regression showed that  
24 461 favipiravir was significantly ( $p = 0.026$ ) associated with faster viral clearance. Additionally the  
25 462 timing of antiviral therapy reached near significance ( $p = 0.055$ ). (19) Furthermore, it was  
26 463 superior to Arbidol in having a higher 7-day clinical recovery rate in patients with COVID-19  
27 464 and a more significant reduction in fever and cough (15). A Japanese observational study  
28 465 assessed the safety and efficacy of favipiravir. The median duration of therapy was 11 days, with  
29 466 reported clinical improvement rates at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%,  
30 467 and 40.1% and 60.3% for mild, moderate, and severe disease, respectively. (24) A prospective,  
31 468 randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-  
32 469 19 chose the primary endpoint was viral clearance by day 6. The secondary endpoint was a  
33 470 change in viral load by day 6. Additionally, exploratory endpoints included time to  
34 471 defervescence and resolution of symptoms. (25) A trial from Russia enrolled 60 patients (40 on  
35 472 favipiravir and 20 on Supportive Care) with primary endpoint as viral elimination. The  
36 473 secondary endpoints were defervescence and RT-PCR negativity. (13) Lately, a phase 3, open-

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3 474 label, randomized, multicenter study (Glenmark Pharmaceuticals) was initiated in India. The  
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5 475 primary endpoint was time until the cessation of oral shedding of the SARS-CoV-2 virus. (26)  
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7 476 According to a study by Jones et al., there are 630 registered trials for COVID-19 on the  
8  
9 477 clinicaltrials.gov website by 1 May, 2020. Most of these trials are from Europe, the USA, China,  
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11 478 and other Asian countries. Additionally, all the trials on the drugs or biologics (218) are studying  
12  
13 479 drugs like hydroxychloroquine or chloroquine (88), azithromycin (53), and 25 trials assessing  
14  
15 480 convalescent plasma, lopinavir/ ritonavir, stem cell treatments, and tocilizumab. (27)  
16

17 482 Another study reported 201 trials registered with the US registry and WHO clinical trials  
18  
19 483 registry platform. Out of these, 93.5% studied drug intervention. From the total trials, 49.8%  
20  
21 484 were from China, 37.8% USA accounting for 87.6% of both countries studies. From the 201  
22  
23 485 trials, only 11 trials are being done on Favipiravir. (28) As of 23 July 2020, there are 32 studies  
24  
25 486 registered on clinicaltrials.gov to assess this drug's utility in the management of COVID-19 (3  
26  
27 487 completed, 12 recruiting). (29)

28 488 Many clinical trials conducted in China, Japan, Russia, and India had an open-label design,  
29  
30 489 which leads to reporting biased results. (13, 19, 25, 26) Recently a study was done in India on  
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32 490 Favipiravir in mild to moderate COVID-19 Cases. This was a randomized, open-label study and  
33  
34 491 the sample size of only 150 patients. (30) There are certain limitations reported in this study,  
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36 492 which were due to the small sample size. The hazard ratio reported was small, and due to the  
37  
38 493 study's open-label nature, it may have been subjected to potential bias. This study's primary  
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40 494 endpoint was confounded due to interpretation issues with RT-PCR positivity and its lack of  
41  
42 495 correlation with the clinical cure. (30)

43 496 A systemic review and meta-analysis of Favipiravir reported evidence showing potential benefits  
44  
45 497 of this drug in clinical and imaging improvement after treating COVID-19 patients. Therefore  
46  
47 498 there is a need for additional randomized, double-blind clinical trials to form a definite opinion  
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49 499 about the rationale to use this drug. There were several drawbacks to the studies that have  
50  
51 500 already been published, such as non-randomized design, small sample sizes, and different  
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53 501 durations of treatment, different dosage regimes, and lack of blinding. (31)  
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55 502  
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57 503 In our study, we adopted the design double-blind, placebo-controlled randomized study, which  
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59 504 provides the best evidence of causation. (32) Randomized double-blind placebo control studies  
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3 505 (RDPCS) are regarded as the “gold standard” of epidemiologic studies. They are employed to  
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5 506 illustrate superiority, equivalence, and non-inferiority. Well-designed RDPCS gives the most  
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7 507 robust possible evidence of causation. The benefits of randomization are 1. It avoids selection  
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9 508 bias that may happen if either the physician or the patient decides the treatment, 2. It removes  
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11 509 most confounding by all known and unknown factors as it prevents an association between the  
12  
13 510 treatment and any other known or unknown factor. Blinding with randomization evades  
14  
15 511 reporting bias as no one is aware of the treatment; hence all treatment groups will be treated the  
16  
17 512 same. The use of placebo as control leads to the placebo effect where the person on placebo will  
18  
19 513 think that they are taking the actual treatment, which leads them to feel better or respond to it due  
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21 514 to wishful thinking. The presence of placebo control will help to compare the drug’s  
22  
23 515 effectiveness against the placebo’s effectiveness (33-35)

24  
25 516 There are currently only two countries (KSA and Kuwait) from the Middle East with ongoing  
26  
27 517 Favipiravir trials with a placebo comparator. (29) Our study is the first trial registered from the  
28  
29 518 Middle East region to date funded by the government of KSA. Our study's sample size is 576  
30  
31 519 subjects, the second largest to Kuwait's trial (780) from the presently ongoing Favipiravir  
32  
33 520 trials.(29)

### 31 521 **LIMITATIONS**

32  
33 522 Numerous challenges are expected during this trial. The trial is ongoing now during restricted  
34  
35 523 travel time, and hospitals restricted nonessential personnel's entry. Protocol training, site  
36  
37 524 initiation visits, and monitoring visits will be performed remotely in many sites. The research  
38  
39 525 team will be assigned to other clinical services, and many members require extra effort. Also,  
40  
41 526 study team member's sicknesses or unprotected exposure to COVID-19 patient strained research  
42  
43 527 resources. Many sites may encounter inadequate supplies of personal protective equipment and  
44  
45 528 trial-related supplies. The study is prone to certain biases due to the design, such as non-  
46  
47 529 compliance, withdrawals after randomization, and attrition/losses to follow-up.

48 530

### 49 531 **ETHICS AND DISSEMINATION**

50  
51 532 This study will be carried out in compliance with the protocol and by the laws and regulations of  
52  
53 533 King Abdullah International Medical Research Centre Ethics Committee (KAIMRC IRB) and  
54  
55 534 the Ministry of Health Ethics Committee (MOH IRB). The date for approval for the first version  
56  
57 535 was 28 April 2020, and for the protocol version, V2.2 is 25 November 2020. KAIMRC IRB

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3 536 approved this study with protocol number RC20/220. The study applies the principles  
4 537 established in the Declaration of Helsinki. The participants will sign a written informed consent  
5 538 form (ICF-supplementary material 2) before the first assessment and data collection by delegated  
6 539 personnel. Contact details of the principal investigator are provided to the patients for queries  
7 540 and concerns. Patients are free to withdraw from the study at any time without any consequences  
8 541 regarding their standard clinical care. Any change or addition to this protocol requires a written  
9 542 amendment approved by the sponsor and the investigators. Before implementation, the  
10 543 investigators will transmit all major amendments to the Ethics Committees, examining the initial  
11 544 protocol. The investigators will transmit a copy of the Ethics Committee's opinion to the sponsor.  
12 545 The investigators will notify all minor amendments to the Ethics Committee that had examined  
13 546 the initial protocol. All amendments will be reported to the clinical trials registration site.  
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## 28 550 **TRIAL STATUS**

29 551 This trial began on 23 July 2020. On 3 March 2021, 191 patients have been enrolled.  
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32

## 33 553 **DATA SHARING PLAN**

34 554 Study protocol and statistical plan will be openly available.  
35  
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## 39 556 **PATIENT AND PUBLIC INVOLVEMENT**

40 557 This research was done without patient and public involvement due to time constraints. The  
41 558 results of the study will be disseminated to the public via social media platforms.  
42  
43  
44  
45

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3 5664  
5 567 Figure 1 Overview of Study

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7 569 Figure 2 Schedule of Enrollment

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10 571 **REFERENCES**11 572 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  
12 573 COVID-19. *The Lancet Infectious Diseases*. 2020;20(6):656-7.13 574 2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease  
14 575 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for  
15 576 Disease Control and Prevention. *JAMA*. 2020.16 577 3. Worldometers.info. Total Coronavirus Cases in Saudi Arabia [internet]. Dover, Delaware,  
17 578 U.S.A.: Worldometer; 2021 [updated 25 Feb 2021; cited 2021 25 Feb]. Available from:  
18 579 <https://www.worldometers.info/coronavirus/country/saudi-arabia/>.19 580 4. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus  
20 581 infections. *Pharmacology & therapeutics*. 2020;209:107512.21 582 5. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nature*  
22 583 *reviews Drug discovery*. 2020;19(3):149-50.23 584 6. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and  
24 585 emerging RNA viruses. *Antiviral research*. 2018;153:85-94.25 586 7. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA  
26 587 polymerase. *Proceedings of the Japan Academy Series B, Physical and biological sciences*.  
27 588 2017;93(7):449-63.28 589 8. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease  
29 590 (COVID-19) [Internet]. online: Centre For Disease Control and Prevention; 2020 [updated Dec 8,2020;  
30 591 cited 2021 18 Jan]. Available from: [https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html)  
31 592 [management-patients.html](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).32 593 9. COVID-19. Coronavirus Disease Guidelines [online]. Kingdom of Saudi Arabia: Ministry of Health;  
33 594 2020 [cited 2021 18 Jan]. Available from:  
34 595 <https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx>.35 596 10. Compendium of Guidelines, Instruction and Standard Operative Procedures for Covid-19  
36 597 [Internet]. India: Medical Education and Drugs Department Government of Maharashtra; 2020 [cited  
37 598 2021 18 Jan]. 4:[Available from:  
38 599 [https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volum](https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volume%204.pdf)  
39 600 [e%204.pdf](https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volume%204.pdf).40 601 11. Ratanarat R, Sivakorn C, Viarasilpa T, Schultz MJ. Critical Care Management of Patients with  
41 602 COVID-19: Early Experience in Thailand. *Am J Trop Med Hyg*. 2020;103(1):48-54.42 603 12. Interim guidelines. Prevention, diagnostics and treatment of a new coronavirus infection  
43 604 (COVID-19) [Internet]. Russia: MOH of the Russian Federation; 2020 [updated 28 April 2020; cited 2021  
44 605 18 Jan]. 6:[Available from: [https://static-](https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf)  
45 606 [1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020\\_%D0%9CR\\_COVID-](https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf)  
46 607 [19\\_v6.pdf](https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf).47 608 13. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the  
48 609 treatment of COVID-19. *International Journal of Infectious Diseases*. 2021;102:501-8.49 610 14. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal*  
50 611 *Medicine*. 2013;158(3):200-7.

- 1  
2  
3 612 15. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A  
4 613 Randomized Clinical Trial. medRxiv. 2020:2020.03.17.20037432.
- 5 614 16. Favipiravir: Report on the Deliberation Results;. 2014. Japan: Toyama Chemical, Evaluation and  
6 615 Licensing Division PaFSBMoH, Labour and Welfare; 2014 March 4 Report No.
- 7 616 17. Heritier SR, Gebiski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-  
8 617 treat principle. *The Medical journal of Australia*. 2003;179(8):438-40.
- 9 618 18. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res*. 2011;2(3):109-12.
- 10 619 19. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for  
11 620 COVID-19: An Open-Label Control Study. Engineering (Beijing, China). 2020.
- 12 621 20. Kumar A, Chakraborty BS. Interim analysis: A rational approach of decision making in clinical  
13 622 trial. *J Adv Pharm Technol Res*. 2016;7(4):118-22.
- 14 623 21. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental  
15 624 Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm  
16 625 Proof-of-Concept Trial in Guinea. *PLoS medicine*. 2016;13(3):e1001967.
- 17 626 22. Bai CQ, Mu JS, Kargbo D, Song YB, Niu WK, Nie WM, et al. Clinical and Virological Characteristics  
18 627 of Ebola Virus Disease Patients Treated With Favipiravir (T-705)-Sierra Leone, 2014. *Clinical infectious  
19 628 diseases : an official publication of the Infectious Diseases Society of America*. 2016;63(10):1288-94.
- 20 629 23. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with  
21 630 Pneumonia in China, 2019. *New England Journal of Medicine*. 2020;382(8):727-33.
- 22 631 24. James MI. Preliminary report of favipiravir observational study in Japan released. online: News-  
23 632 Medical.net, 2020.
- 24 633 25. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A Prospective,  
25 634 Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with  
26 635 COVID-19. *Antimicrobial Agents and Chemotherapy*. 2020;64(12):e01897-20.
- 27 636 26. Singh P. A Clinical Study on Favipiravir Compared to Standard Supportive Care in Patients With  
28 637 Mild to Moderate COVID-19 [Online]. *Cochrane COVID-19 Study Register2020* [updated April ]. Version  
29 638 3 [Available from: ICTRP (<http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43504>)].
- 30 639 27. Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered  
31 640 with ClinicalTrials.gov: cross-sectional analysis. *BMJ Open*. 2020;10(9):e041276.
- 32 641 28. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical  
33 642 trials assessing treatments for COVID-19: a cross-sectional analysis. *BMJ Open*. 2020;10(6):e039978.
- 34 643 29. Listed COVID 19 Studies [Internet]. online: US National Institute of Health (NIH); 2020 [cited 2020  
35 644 26 Nov]. *Clinicaltrials.org*. Available from: <https://www.clinicaltrials.gov>.
- 36 645 30. Udawadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and Safety of  
37 646 Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A  
38 647 Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial. *International Journal of  
39 648 Infectious Diseases*. 2020.
- 40 649 31. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other  
41 650 antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis.  
42 651 *Virology journal*. 2020;17(1):141.
- 43 652 32. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best  
44 653 observational study. *BMJ*. 2000;321(7256):255-6.
- 45 654 33. Oleckno WA. *Essential Epidemiology: Principles and Applications*. 4180 IL route 83, suite 101  
46 655 Long Groove, IL: Waveland Press, Inc.; 2002.
- 47 656 34. Hulley S, Cummings S, Browner W, Grady D, Newman T. *Designing clinical research*. 503 Walnut  
48 657 street, Philadelphia, PA, USA: Williams and Wilkins .A Walters Kluwer business Lippincot; 2007.
- 49 658 35. Manja V, Lakshminrusimha S. *Epidemiology and Clinical Research Design, Part 1: Study Types*.  
50 659 *Neoreviews*. 2014;15(12):e558-e69.

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3 660  
45 661 **AUTHOR CONTRIBUTIONS**

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

667

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

671

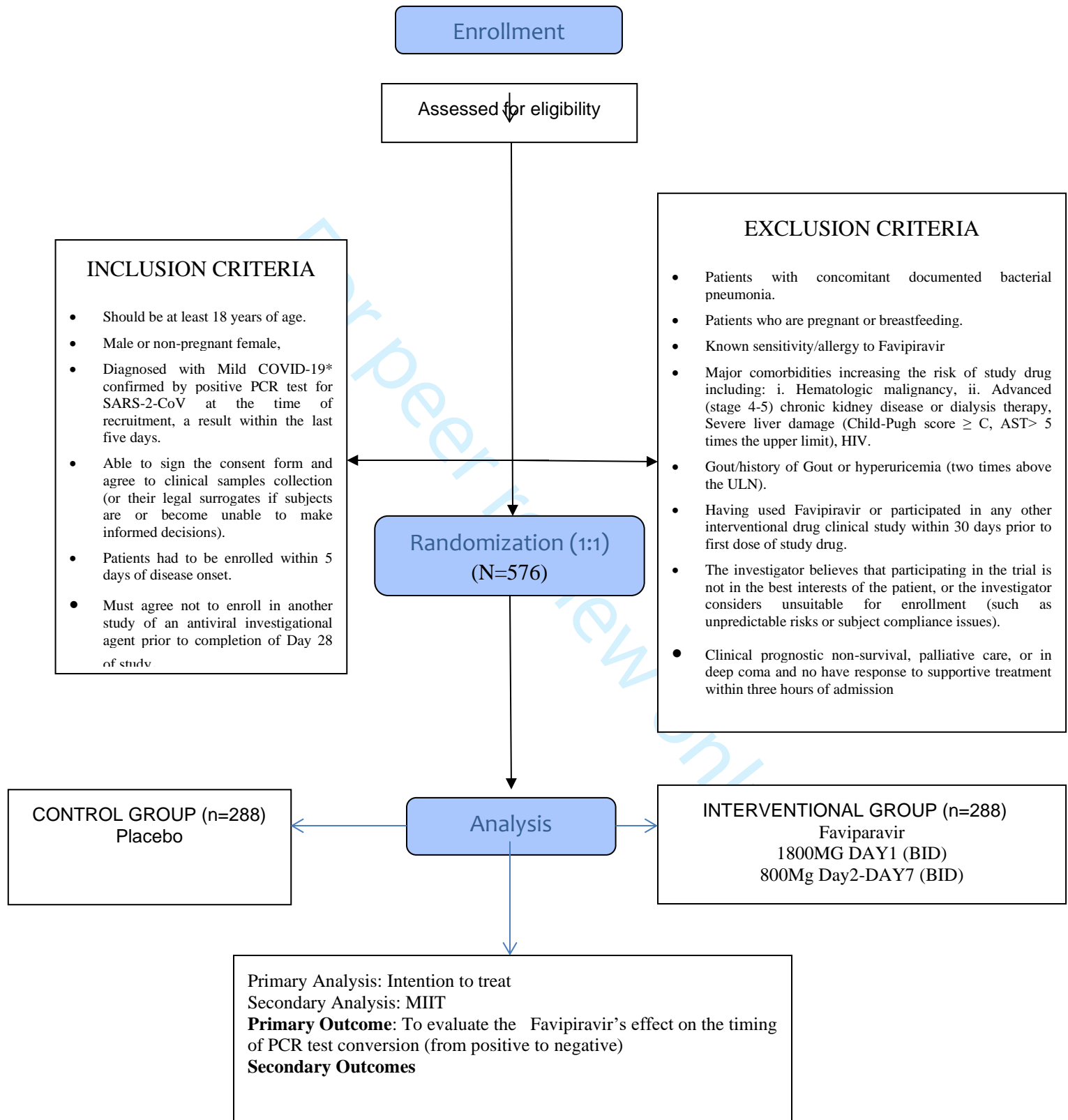
672 **COMPETING INTERESTS**

673 Authors declare no competing interest.

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

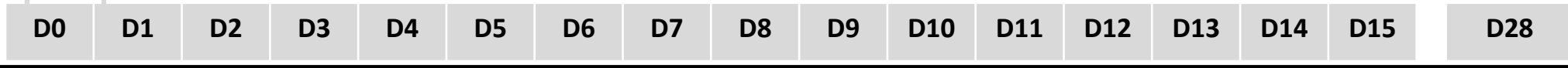


Eligibility assessment  
 Informed consent  
 Randomization  
 Baseline data

Administration of Study Drug:  
 Favipiravir/Placebo  
 Adverse Drug Reactions Assessment

Daily follow-up/ Symptoms Evaluation

Serious Adverse Events Assessment



Medical History

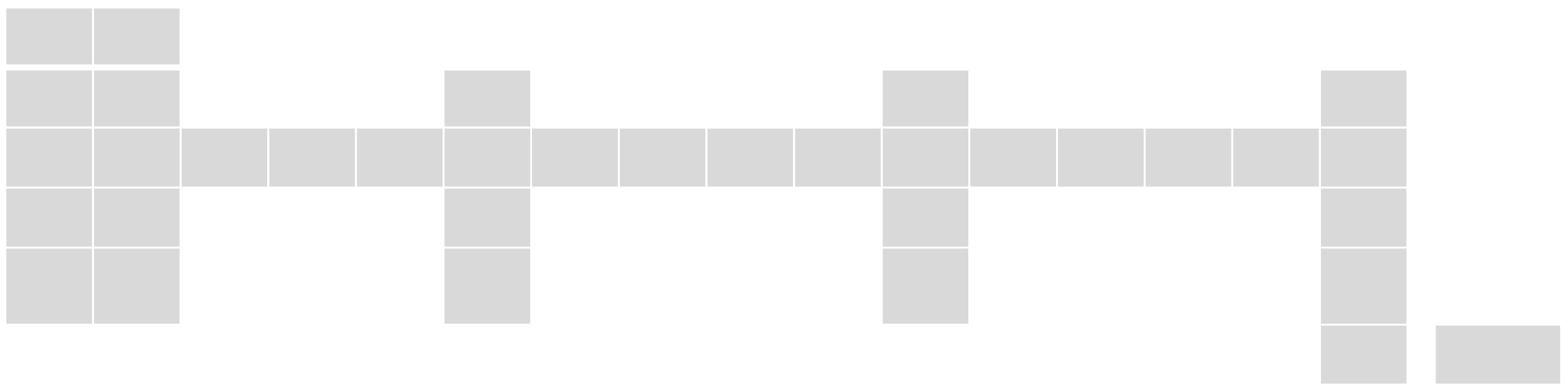
Vital Signs

Clinical Data Collection

SARS-CoV-2 Testing

Blood Tests  
 (CBC, Renal Profile & LFT)

Outcome



# 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  $\geq$  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

1 7.The investigator believes that participating in the  Yes  No  
2 trial is not in the best interests of the patient,  
3 or the investigator considers unsuitable for  
4 enrollment (such as unpredictable risks or subject  
5 compliance issues)

8 8.Clinical prognostic non-survival, palliative care,  Yes  No  
9 or in deep coma and have no response to supportive  
10 treatment within three hours of admission

13 Randomization

16 Site  Site1  
17  Site2  
18  Site3  
19  Site4  
20  Site5  
21  Site6  
22  Site7  
23  Site8  
24  Site9  
25  Site10

27 Patient Recruited in ?  Hospital  
28  Community

30 Treatment  A  
31  B  
32  C  
33  D

35 Randomization Time

For peer review only

# Co-Morbidities

1  
2  
3  
4  
5 Height

6 \_\_\_\_\_  
7 (cm)  
8

9 Weight

10 \_\_\_\_\_  
11 (kg)  
12  
13

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

	Yes	No	NA
17 Hypertension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18 Chronic cardiac disease, 19 including congenital heart 20 disease (not hypertension)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21 22 Chronic pulmonary disease (not 23 asthma)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24 25 Asthma (physician diagnosed)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
26 27 Chronic kidney disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
28 29 Chronic liver disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 31 Chronic neurological disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
32 33 Chronic 34 Rheumatologic/Auto-immune 35 disorder	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
36 37 Obesity (BMI more than 30)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
38 39 Diabetes with complications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
40 41 Diabetes without complications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
42 43 Smoking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
44 45 Other	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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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
8 Fever	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9 Cough	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10 Cough with Sputum Production	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11 Cough with Bloody Sputum/Haemoptysis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12 Sore Throat	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13 Runny Nose (Rhinorrhoea)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14 Chest Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15 Shortness of Breath (Dyspnea)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16 Loss of smell	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17 Loss of taste	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18 Abdominal Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19 Vomiting / Nausea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20 Diarrhoea	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21 Ear Pain	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22 Muscle Aches (Myalgia)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
23 Joint Pain (Arthralgia)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24 Fatigue / Malaise	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25 Lower Chest Wall Indrawing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
26 Headache	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
27 Conjunctivitis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
28 Skin Rash	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
29 Skin Ulcers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 Lymphadenopathy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

For peer review only

# Daily Clinical Assessment

**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)

1 Systolic Blood Pressure \_\_\_\_\_  
2  
3 (mmHg)

5 Diastolic Blood Pressure \_\_\_\_\_  
6  
7 (mmHg )

10 Mean Arterial Blood Pressure \_\_\_\_\_  
11  
12 (mmHg )

14 Urine flow rate \_\_\_\_\_  
15  
16 (mL/24 hours Check if estimated )

18 Glasgow Coma Score (GCS / 15) \_\_\_\_\_  
19  
20

**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
26 Non-invasive ventilation (e.g. BIPAP, CPAP)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
29 Invasive ventilation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 Extra corporeal life support (ECLS)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
32 High-flow nasal cannula oxygen therapy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
34 Dialysis/Hemofiltration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
36 Any vasopressor/inotropic support	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

38 Progress of Symptoms at 1st Presentation(pyrexia, short of breath, and relief of cough and/or others)  
39 Can stop recording if resolved for 72 hours  
40  
41  Worsening  
42  Same  
43  Better  
44  Resolved

**Signs and Symptoms**

46 New signs and symptoms  Yes  No

49 Specify, \_\_\_\_\_  
50  
51 (L/min)

53 Starting Date \_\_\_\_\_  
54  
55

57 Fever  Yes,  No



1 Fever Result

2  
3 \_\_\_\_\_  
4 (°C)

5 Any hospital/ER visits

6  Yes  No

7  
8  
9 Was Vital Signs Collected?

10  Yes  No

11  
12  
13  
14 Temperature

15 \_\_\_\_\_  
16 (°C)

17  
18 Heart Rate

19 \_\_\_\_\_  
20 ( Beat Per Minut)

21  
22  
23 Respiratory Rate

24 \_\_\_\_\_  
25 (Breath Per Minute)

26  
27  
28 Systolic Blood Pressure

29 \_\_\_\_\_  
30 (mmHg)

31  
32 Diastolic Blood Pressure

33 \_\_\_\_\_  
34 (mmHg)

35  
36 Oxygen Saturation

37 \_\_\_\_\_  
38 (%)

39  
40  
41 Oxygen On

42  Room air  Oxygen therapy  
43  NA

44 Specify, Oxygen Therapy

45 \_\_\_\_\_  
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# 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

For peer review only

# 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 ( $\pm 1$  day)  
 Day 10 ( $\pm 1$  day)  
 Day 15 ( $\pm 2$  day)

## Laboratory Assessment

Haemoglobin

\_\_\_\_\_

- g/L    g/dL

WBC Count

\_\_\_\_\_

- $\times 10^9/L$      $\times 10^3/\mu L$

Lymphocyte count

\_\_\_\_\_

(cells/  $\mu L$ )

Neutrophil count

\_\_\_\_\_

(cells/  $\mu L$ )

Platelets

\_\_\_\_\_

- $\times 10^9/L$      $\times 10^3/\mu L$

ALT/SGPT

\_\_\_\_\_

(U/L)

Total Bilirubin

\_\_\_\_\_

- $\mu mol/L$     mg/dL

AST/SGOT

\_\_\_\_\_

(U/L)

Glucose

\_\_\_\_\_

1 \_\_\_\_\_  mmol/L  mg/dL

2

3

4 Blood Urea Nitrogen (urea) \_\_\_\_\_

5

6

7 \_\_\_\_\_  mmol/L  mg/dL

8

9 \_\_\_\_\_  mmol/L  mg/dL

10

11

12 Creatinine \_\_\_\_\_

13

14

15 \_\_\_\_\_  umol/L  mg/dL

16

17 Sodium \_\_\_\_\_

18

19 (mEq/L)

20

21

22 Potassium \_\_\_\_\_

23

24 (mEq/L)

25

26 Chest X-Ray performed?  Yes  No  NA

27

28

29 Were Infiltrates Present?  Yes-Unilateral  Yes - Bilateral

30  No  NA

31

32

33

34

35  Yes

36 ECG performed?  No

37  N/A

38

39 if YES QT Interval \_\_\_\_\_

40

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# Daily Study Drug

## Favipiravir / Placebo

Was Favipiravir given?

- Yes
- No

Dose

\_\_\_\_\_

Dose Number

\_\_\_\_\_

Date

\_\_\_\_\_

Time given

\_\_\_\_\_

Drug Method

- Syrup
- tablet

For peer review only

# 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	<input type="radio"/>	<input type="radio"/>
Bacterial Pneumonia	<input type="radio"/>	<input type="radio"/>
Coagulopathy	<input type="radio"/>	<input type="radio"/>
Acute lung Injury/ARDS	<input type="radio"/>	<input type="radio"/>
Anemia	<input type="radio"/>	<input type="radio"/>
Pneumothorax	<input type="radio"/>	<input type="radio"/>
Pleural Effusion	<input type="radio"/>	<input type="radio"/>
Acute renal Injury/Failure	<input type="radio"/>	<input type="radio"/>
Seizure	<input type="radio"/>	<input type="radio"/>
Congestive Heart Failure	<input type="radio"/>	<input type="radio"/>
Meningitis/ Encephalitis	<input type="radio"/>	<input type="radio"/>
Stroke/Cerebrovascular Accident	<input type="radio"/>	<input type="radio"/>
Endocarditis / Myocarditis / Pericarditis	<input type="radio"/>	<input type="radio"/>
Cardiac Arrhythmia	<input type="radio"/>	<input type="radio"/>
Bacteremia	<input type="radio"/>	<input type="radio"/>
Cardiac Arrest	<input type="radio"/>	<input type="radio"/>
Liver Dysfunction	<input type="radio"/>	<input type="radio"/>
Rhabdomyolysis / Myositis	<input type="radio"/>	<input type="radio"/>
Other	<input type="radio"/>	<input type="radio"/>

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



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Last/End Date

\_\_\_\_\_

OTHER Intervention or Procedure

\_\_\_\_\_

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# 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

\_\_\_\_\_

1 Azithromycin\_end date \_\_\_\_\_  
2  
3 \_\_\_\_\_  
4  
5 Interferon Dose \_\_\_\_\_  
6  
7 \_\_\_\_\_  
8 Interferon\_Start date \_\_\_\_\_  
9  
10 \_\_\_\_\_  
11 Interferon\_End date \_\_\_\_\_  
12  
13 \_\_\_\_\_  
14 Oseltamivir Dose \_\_\_\_\_  
15  
16 \_\_\_\_\_  
17  
18 Oseltamivir\_Start date \_\_\_\_\_  
19  
20 \_\_\_\_\_  
21 Oseltamivir\_End date \_\_\_\_\_  
22  
23 \_\_\_\_\_  
24 Anti-Interleukin-6 Agents?  Yes  No  
25  
26  
27  
28 Please ,Provide Type \_\_\_\_\_  
29  
30 \_\_\_\_\_  
31 Please ,Provide the Dose \_\_\_\_\_  
32  
33 \_\_\_\_\_  
34 Antibiotic?  Yes  No  NA  
35  
36  
37  
38 Dose \_\_\_\_\_  
39  
40 \_\_\_\_\_  
41 Type \_\_\_\_\_  
42  
43 \_\_\_\_\_  
44 Is the patient take another antibiotic?  Yes  No  NA  
45  
46  
47  
48 Antibiotic\_2 Type \_\_\_\_\_  
49  
50 \_\_\_\_\_  
51  
52 Antibiotic\_2 Dose \_\_\_\_\_  
53  
54 \_\_\_\_\_  
55 Antibiotic\_3 Type \_\_\_\_\_  
56  
57 \_\_\_\_\_  
58 Antibiotic\_3 Dose \_\_\_\_\_  
59  
60 \_\_\_\_\_

For peer review only

1 Antibiotic\_4 Type \_\_\_\_\_  
2  
3 \_\_\_\_\_  
4 Antibiotic\_4 Dose \_\_\_\_\_  
5  
6 \_\_\_\_\_  
7  
8 Convalescent plasma?  Yes  No  N/A  
9  
10  
11 Specify \_\_\_\_\_  
12  
13 \_\_\_\_\_  
14 Corticosteriod?  Yes  
15  No  
16  
17  
18  
19 Dose \_\_\_\_\_  
20  
21 \_\_\_\_\_  
22  
23 Type \_\_\_\_\_  
24  
25 \_\_\_\_\_  
26 Duration \_\_\_\_\_  
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For peer review only

# Outcome

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## Outcome at Day 14

Outcome at day 14:

- Alive
- Hospitalization
- Transfer to other facility
- Death
- Unknown

Outcome Date

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Hospital Discharge Date

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## Outcome at Day 28

Outcome at Day 28

- Alive
- Death

Outcome Date

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FO peer review only

# 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

1 OtherI  No  1  2  3  
 2  4  5

4 Specify, \_\_\_\_\_  
 5  
 6

8 OtherII  No  1  2  3  
 9  4  5

11 Specify, \_\_\_\_\_  
 12  
 13

15 **Central Nervous System**

17 Headache  No  1  2  3

20 Insomnia  No  1  2  3

23 Psychosis  No  1  2  3  
 24  4  5

27 Depression  No  1  2  3  
 28  4  5

30 Mania  No  1  2  3  
 31  4  5

33 ECG: QT Interval Changes  No  1  2  3  
 34  4  5

37 OtherI  No  1  2  3  
 38  4  5

40 Specify, \_\_\_\_\_  
 41  
 42

43 OtherII  No  1  2  3  
 44  4  5

46 Specify, \_\_\_\_\_  
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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 1<sup>st</sup> 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

1 suspected pregnant females in this study.  
2  
3

#### 4 **9. Costs and compensation for participation in this study:**

5  
6 You will not receive any compensation for your participation in this trial. However, in the event of  
7 an illness or injury related to the study medication, all treating procedures, follow-ups,  
8 hospitalization, will be provided to you immediately.  
9

#### 10 **10. Benefits:**

11  
12 Previous studies done in USA and JAPAN have shown that this medication had a positive effect in  
13 treating influenza virus.  
14

15  
16 You may or may not benefit directly from participating in this research, but your participation may  
17 help other patients with COVID-19.  
18

19  
20 This research study will increase the medical knowledge which will help to decide if  
21 FAVAPIRAVIR medication can be used in treatment of COVID-19 in the future.  
22  
23

#### 24 **11. Alternative Treatment(s):**

25  
26 You will be receiving the routine treatment as per the treating physicians during the course of the  
27 study and you will be made aware of any new treatment available for the disease.  
28  
29

#### 30 **12. Information about participation:**

31  
32 Your participation in this study is totally voluntary, you have the right to withdraw at any time you  
33 want without mentioning the reasons. If you do not want to take part, you will receive standard care  
34 provided by your doctor, and your decision about the study will not affect your current or future  
35 medical care.  
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38 The study doctor and the study sponsor have the right to withdraw you from the study if he decided  
39 that it's better for your medical condition. Or you did not comply with study requirements.  
40

41 If you have any other diseases or adverse events the principal investigator will decide whether to  
42 continue with participation in the study or not.  
43  
44

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

46  
47 All information related to you including personal and medical data provided and collected by the  
48 study doctor and recorded in the study records will be handled as confidential and no one except  
49 authorized research team at King Abdullah International Medical Research Center (KAIMRC),  
50 Sponsors, Institutional Review Board (IRB), Research Scientific Committee (RC), Ministry of  
51 Health auditors, the Saudi Food and Drug Administration (SFDA) and related personnel that can  
52 have access to record, review and analyze them.  
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55 All the information collected in subjects records belong to King Abdullah International Medical  
56 Research Center. In case any results of the study are published, your personal information will never  
57 be mentioned, it may be coded in symbols known for research team  
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#### 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.

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



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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

1	<b>Introduction</b>			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	4
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	4
7				
8	Objectives	7	Specific objectives or hypotheses	10
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	6
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	8
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	11
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	9
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
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34	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	
35			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	10
36			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
37			efficacy and harm outcomes is strongly recommended	
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40	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	8
41			participants. A schematic diagram is highly recommended (see Figure)	
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1	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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
5				

## 6 **Methods: Assignment of interventions (for controlled trials)**

### 7 Allocation:

8				
9				
10	Sequence	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
11	generation			
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16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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## 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	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
34	methods			
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39		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
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1	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
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5	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
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
9				
10		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
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14	<b>Methods: Monitoring</b>			
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16	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
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22		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
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25	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
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
35				
36				
37	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
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
11				
12				
13	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
14				
15				
16	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
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19				
20	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
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
32				
33				
34	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
35				
36				

\*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”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.