PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol:A Multicentre Randomized Double-Blinded Placebo-Controlled Trial of Favipiravir in Adults with Mild Coronavirus Disease COVID-19
AUTHORS	Bosaeed, Mohammad; Alharbi, Ahmad; hussein, Mohammad; Abalkhail, Mohammed; Sultana, Khizra; Musattat, Abrar; Hajar Alqahtani, Hajar Alqahtani; Alshamrani, Majid; Mahmoud, Ebrahim; Alothman, Adel; Alsaedy, Abdulrahman; Aldibasi, Omar; Alhagan, Khalid; Asiri, Abdullah; AlJohani, Sameera; Al-Jeraisy, Majed; Alaskar, Ahmed

VERSION 1 – REVIEW

REVIEWER	Hanna, Catherine University of Glasgow, CRUK Clinical Trials Unit
REVIEW RETURNED	18-Dec-2020

GENERAL COMMENTS	This submission describes a protocol for a clinical trial investigating treatment for Covid-19. It is clearly hugely topical and this manuscript will help to communicate ongoing studies in this field. The authors have made the effort to submit their protocol for publication which will allow comparability between other studies in the field and help to increase transparency around the trials that are planned or ongoing to tackle Covid-19. There are several issues that need to be addressed before this can be published. <u>Major issues</u> 1. The authors mention the trial's secondary objectives but do not give any information on the endpoints that will be investigated to meet these objectives. It would be useful to know what information is being collected, at what time points it will be collected and how it will be analysed to meet these objectives. For example, it is not clear what tool will be used to assess safety/adverse events. Also, line 236 mentions that a patient will be followed up until they meet a secondary endpoint but it is not clear what exactly this endpoint entails. 2. It would be useful to know why this dose and duration of favipiravir was chosen and who/which company will supply the drug. Other information that is missing includes: how many and which centres will recruit to the trial, who is funding the trial and what input did they have to the trial design, are there any prohibited medications, are patients allowed to participate in other trials at the same time and what are the criteria for unblinding? Although mentioned on line 145, it would be useful to make clearer if the trial setting

	is in hospital or the community. 3. The authors mention that the trial updates will be posted to clinicaltrials.gov. Please include the link to where the trial is registered on clinicaltrials.gov rather than the generic web address (line 85). 4. Line 131/132 says that favipiravir "was listed in many guidelines as a treatment option and ongoing trials and ongoing trials assessing its efficacy and safety". Please provide more information or reference which guidelines and which trials. Also, I think the text was perhaps meant to read "…there are ongoing trials…". 5. In line 197, the authors say the trial consists of three main parts: screening, treatment and follow-up period. Please describe in more detail what time lines are involved/assessments will be done in each part. 6. Line 203 states, "when multiple assessments are taken at the same time point, the most out-of-range value will be taken." Please explain what is meant by this statement, perhaps by giving an example. 7. In Table 1, please clarify what "baseline data" refers to. 8. I appreciate that the trial end-point is finalised however it would be useful to know why the endpoint of a reduction in time to viral clearance was chosen. Do the authors feel this is clinically relevant and has it been tested in other trials? This could be addressed in the discussion. 9. I have made a separate comment in the review proforma to say that this manuscript does require separate statistical review. 10. Please provide more detail about the placebo. Currently, figure 1 implies that patients will receive 1800mg /800mg of placebo but it is not clear if this is a medication or if not, why there is a dose given. 11. In the discussion the authors list other trials that are testing favipiravir for Covid-19. It would be useful if the discussion included more reflection on their choice of endpoint compared to other trials and why more trials such as theirs are needed in the context of results already published. For example, line 291 states that the study design eliminates bias – can the authors expand on this statement and indicate why their design in particular eliminates bias and which bias they are referring to. 12. The authors have used a CONSORT diagram and checklist to summarise the trial protocol but this is usually reserved for when reporting trial recruitment/outcomes. A SPIRIT reporting checklist would be more appropriate to a trial protocol. If all parts of the SPIRIT checklist were addressed, this would fill many of the current gaps in the manuscript. A separate flow diagram for the trial schema could be provided alongside the SPIRIT checklist. <u>Minor issues</u> 1. There are several typing errors, for example, the use of capital letters in the middle of sentences, different size fonts in the table, extra commas, lack of full stops (for example line 118). There are several abbreviations that have not been spelled out in full on first use (for example line 238). There are also several abbreviations in

	the Table. 2. The authors comment that patient and public involvement was “not appropriate”. I wonder if they are implying that there was not sufficient time or resources to involve patients in the design of the trial protocol rather than it being inappropriate to do so. 4. Covid-19 is not consistently referenced in the manuscript – for example, COVID19, Covid-19, COVID-19, COVID 19. 5. Please provide the date the study/protocol was approved by the named ethics committee. 6. Line 368 and 373, please provide reference numbers for the review articles cited. 7. Statement on line 389 that the trial provides high quality evidence is misleading as there are no trial results being reported in this manuscript.

REVIEWER	Emadi, Ashkan University of Maryland Baltimore, School of medicine
REVIEW RETURNED	24-Dec-2020

GENERAL COMMENTS	Major Comments: 1) In the abstract the sample size is 634 (317 per arm), but in the Strengths and Limitations is 576. 2) Exclusion criterion #2: how do the investigators establish the presence or absence of "bacterial" pneumonia? 3) Exclusion criterion #3 & 6: Are patients with previous exposure to favipiravir and without allergy allowed to be enrolled? if not, how does one know about "known" history of hypersensitivity/allergy? 4) Are hospitalized patients excluded? 5) Please define your primary and secondary "objectives" as well as primary and secondary "endpoint(s)". 6) I suggest to monitor only the relevant concomitant medications. Monitoring all medications will be a huge tasks for the clinical research office and data managers and often it is not necessary. 7) Please clarify who is responsible for the randomization? and who is unblinded to ultimately know which patient receives what? 8) Please clarify how placebo is made? and who is making it? Is it centralized in one site and distributed to the other sites? 9) Who is responsible for obtaining the swabs, the clinical team or the research team? 10) How often DSMB will meet? What are the criteria for unblinding the study? 11) Please explain the potential causes of false positive and false negative. 12) It would be very interesting to discuss whether cost/risk-benefit of 2 days improvement in viral clearance in mild cases favorable or clinically meaningful? Minor comments: Please change the typescript as below: 1) Title: change "placebo control" to "placebo-controlled" 2) COVID19 should be consistent in the entire typescript. For example, on line 52 & 113 it is "Covid-19" and on line 58 is "COVID19" and on line 62 & 113 it is "COVID-19" 3) several words in the middle of sentences are started with capital letters. Please correct them.

	4) On lines 118 & 119 finish the sentences with ".". 5) Inclusion criteria 3 and 4 are redundant

REVIEWER	Nanni, Oriana IRST IRCCS, Clinical Trial
REVIEW RETURNED	31-Dec-2020

GENERAL COMMENTS	Minor revision/comments: - Pag 5 line 152: which concomitant treatment are permitted? since there is a placebo control group, the definition of concomitant treatments allowed is very important - Pag 5 line 152 It is unclear whether the patient with mild COVID-19 should or can be hospitalized at screening phase and during treatment : if not, how he/she is managed? (Mobile team?) - Pag 5 line 152: "Male or non-pregnant female " implies that the pregnancy test is mandatory - Pag 10 line 271 -275 the : the difference in the definition of ITT and modified ITT is not clear Based on the emerging evidence, I invite you to pay close attention to the time between the onset of symptoms and the start of therapy. a post-hoc analysis might be useful

VERSION 1 – AUTHOR RESPONSE

Reviwer 1
Major issues
1. a. The authors mention the trial's secondary objectives but do not give any information on the endpoints that will be investigated to meet these objectives. It would be useful to know what information is being collected, at what time points it will be collected and how it will be analysed to meet these objectives. . Also, line 236 mentions that a patient will be followed up until they meet a secondary endpoint but it is not clear what exactly this endpoint entails.
The following information is added to the manuscript
ϖ Endpoints selection is based on the objectivity and to present the most reliable to assess mild infection. It is expected that the majority of the cases would be mild. Therefore, the markers used (viral clearance), which capture the viral shedding duration and possible contagiousness period, reflect the best assessment for such a spectrum.
ϖ To evaluate Favipiravir's effect on clinical recovery. This is assessed by evaluating the duration from start of treatment (Favipiravir or placebo) to normalization of pyrexia, respiratory symptoms, and relief of cough (or other relevant symptoms at enrollment) that is maintained for at least 72 hours.

ϖ Evaluate symptoms severity and the progression in the disease course in both arms till 28 days after starting medicine. Time Frame: 28 days after taking medicine
ϖ To evaluate Favipiravir's effect on the requirement of the use of antipyretics, analgesics, or antibiotics within 15 days after starting medicine. Time Frame: 15 days after taking medicine.
ϖ To evaluate Favipiravir's effect on disease complications within 28 days after starting medicine (Time frame: hospitalization, ICU admission or Mechanical ventilation 28 days after starting medication).
ϖ Evaluate the safety of investigational therapeutics as compared to the control arm within 15 days after starting medicine. This is assessed by allergic reactions, medication intolerance, liver toxicity,

and hyperuricemia I subjects. [Time Frame: 15 days after taking medicine]

1. b. For example, it is not clear what tool will be used to assess safety/adverse events
Following information is added to the manuscript:
ϖ For assessing the safety/adverse events will be reported on the e-CRF in the 'REDCAP' database. Whether or not associated with study medication administration, adverse events will be recorded on the Adverse Event form of the e-CRF. We have added the time frame and details about the secondary end point.
2. a. It would be useful to know why this dose and duration of favipiravir was chosen.
ϖ This dose was chosen based on the drug insert provided for the medication from the studies that were done in Japan. The current recommended regimen of favipiravir is 1800 mg of loading dose BID on day 1 followed by 800 mg BID from day 2 (Fabiflu Prescribing Information). And according to the following published report.
ϖ Following reference has been added to the manuscript.

1.-Avigan® Tablet 200 mg- Deliberation Results by PMDA. (2014). Favipiravir: Report on the Deliberation Results; Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau; Ministry of Health, Labour and Welfare; March 4, 2014. Avigan® is registered brand name of the innovator)
2. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases. 2021;102:501-8.
2. b. who/which company will supply the drug?
The sponsor has imported the placebo from FujiFilm Toyama Chemical Co. and Zhejiang Hisun Pharmaceutical co., Ltd

2. c. Other information that is missing includes: how many and which centers will recruit to the trial,?
ϖ Presently there are 7 centers including the sponsor site. Ministry National Guard Health Affairs (MNGHA) Riyadh, Primary Health Care(PHC)- Mansoura and PHC-Al Urijah Riyadh, MNGHA Madinah and PHC Safiyah -Madinah, King Fahad Hospital -Madinah, King Abdullah Medical City-Makkah,
2. d. Who is funding the trial and what input did they have to the trial design,
ϖ This trial is funded by King Abdullah International Medical Research Center-This information was added at the end of the manuscript. The sponsor provided the expert professionals for writing and executing the protocol.
2. e. Are there any prohibited medications?
ϖ Yes, any type of Antiviral medication is prohibited.
2. f. Are patients allowed to participate in other trials at the same time?
ϖ No the patients are not allowed to participate in other trials as per the study protocol.
2. g. What are the criteria for unblinding?
ϖ The unblinding will be carried out according to the attached appendix.

2. h. Although mentioned on line 145, it would be useful to make clearer if the trial setting is in hospital or the community.
ϖ The trial setting is community.
3. The authors mention that the trial updates will be posted to clinicaltrials.gov. Please include the link to where the trial is registered on clinicaltrials.gov rather than the generic web address (line 85).
ϖ The link has been provided in the manuscript as to: https://clinicaltrials.gov/ct2/show/NCT04464408

4. Line 131/132 says that favipiravir "was listed in many guidelines as a treatment option and ongoing trials and ongoing trials assessing its efficacy and safety". Please provide more information or reference which guidelines and which trials. Also, I think the text was perhaps meant to read "…there are ongoing trials…".

Japan, Russia, Saudi Arabia, Thailand, Kenya and India have recommended the usage of favipiravir oral therapy in mild to moderate COVID-19 in the treatment guidelines.(1,2,3,4,5) The screening of a chemical library for antiviral activity against the influenza virus by the Toyama Chemical Co., Ltd led to the discovery of Favipiravir. FUJIFILM and MediVector conducted the worldwide development of this antiviral drug. In 2014, it was approved for medical use in Japan to treat the new reemerging pandemic influenza virus infections. (6)Furthermore, Favipiravir was approved to treat novel influenza in China in February 2020 and is being studied in the Chinese population for experimental treatment of the emergent COVID-19. (7)

ϖ Following references has been added to the manuscript.

1 Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) [Internet]. online: Centre For Disease Control and Prevention; 2020 [updated Dec 8,2020; cited 2021 18 Jan]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

2. COVID-19. Coronavirus Disease Guidelines [online]. Kingdom of Saudi Arabia: Ministry of Health; 2020 [cited 2021 18 Jan]. Available from: https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/covid19.aspx.

3. Compendium of Guidelines, Instruction and Standard Operative Procedures for Covid-19 [Internet]. India: Medical Education and Drugs Department Government of Maharashtra; 2020 [cited 2021 18 Jan]. 4:[Available from: https://www.maharashtramedicalcouncil.in/Files/MEDD%20Compendium%204th%20Edition%20Volume%204.pdf

4. Ratanarat R, Sivakorn C, Viarasilpa T, Schultz MJ. Critical Care Management of Patients with COVID-19: Early Experience in Thailand. Am J Trop Med Hyg. 2020;103(1):48-54

5.Interim guidelines. Prevention, diagnostics and treatment of a new coronavirus infection (COVID-19) [Internet]. Russia: MOH of the Russian Federation; 2020 [updated 28 April 2020; cited 2021 18 Jan]. 6: [Available from: https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/116/original/28042020_%D0%9CR_COVID-19_v6.pdf.

6.Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020 May;209:107512. doi: 10.1016/j.pharmthera.2020.107512. Epub 2020 Feb 22. PMID: 32097670; PMCID: PMC7102570.

7.Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020 Mar;19(3):149-150. doi: 10.1038/d41573-020-00016-0. PMID: 32127666.

5. In line 197, the authors say the trial consists of three main parts: screening, treatment and follow-up period. Please describe in more detail what time lines are involved/assessments will be done in each part.

This has already been mentioned in the manuscript

ϖ Screening: Information that will be collected on the day of enrollment for the patient's demographics and epidemiological factors, comorbidities, vital signs and symptoms will be regarded as baseline data.

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

Follow-up period: The follow- up period starts from the second day after randomization for 14 days where the research coordinator or the physician wills follow-up the patients' health through a phone call. Follow-up of symptoms evaluation should be for 15 days or until patient reaches secondary endpoint (resolving symptoms).

ϖ The patient's assessment will be recorded in the E-CRF. Another follow-up will be made on day 28 days from randomization.

Serial nasopharyngeal/ Oropharyngeal swab samples will be obtained on day 1(-5 days) before therapy was administered. On day's 5±1 day, 10±1day, 15±2days, extra nasopharyngeal/

oropharyngeal PCR COVID-19 samples requested by the treating team will be recorded.
Patients' follow-up and needed laboratory investigations will be done while the patient is in the hospital. If the patient is discharged or in outpatient settings, the follow up evaluation and obtaining specimens will be done through a delegated personnel in the outpatient clinic or mobile team trained as per study protocol.
6. Line 203 states, "when multiple assessments are taken at the same time point, the most out-of-range value will be taken." Please explain what is meant by this statement, perhaps by giving an example.
ϖ When multiple assessments are taken for vital signs or labs for example for blood pressure the value that is out of range or abnormal ie higher or lower than normal rang will be documented.
7. In Table 1, please clarify what "baseline data" refers to.
ϖ The baseline data in our e-CRF refers to the data which is documented for the subject's demographics, comorbid conditions, vital signs, symptoms and epidemiological data collected on the day of enrollment.

8. I appreciate that the trial end-point is finalized however it would be useful to know why the endpoint of a reduction in time to viral clearance was chosen. Do the authors feel this is clinically relevant and has it been tested in other trials? This could be addressed in the discussion.
ϖ During the Ebola virus disease outbreak, the JIKI trial illustrated an improved survival rate in patients with moderate to high viral load with favipiravir. (1) Similarly, Bai et al.'s study proved a significant decline in viral load with favipiravir in patients with moderate viral load at baseline. These findings support the role of favipiravir in viral load reduction. The homology of gene sequences of SARS-CoV-2 and SARS was over 90%, (3) it is expected that the intervention of antiviral drugs in COVID-19 patients will likely improve or shorten the time to viral clearance.
ϖ The reduction in time to viral clearance is chosen as the endpoint based on above evidence. Therefore, the markers used (viral clearance), which capture the viral shedding duration and possible contagiousness period, reflect best assessment. (1,2,4)

Reference:
1.Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med 2016;13
2.Bai CQ, Mu JS, Kargbo D, Song YB, Niu WK, Nie WM, et al. Clinical and virological characteristics of Ebola virus disease patients treated with favipiravir (t-705)- sierra leone, 2014. Clin Infect Dis 2016;63:1288–94
3.N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al.A novel coronavirus from patients with pneumonia in China 2019 N Engl J Med, 382 (2020), pp. 727-733
4.Denis, M., V. Vandeweerd, R. Verbeke, A. Laudisoit, T. Reid, E. Hobbs, L. Wynants and D. V. d. Vliet (2020). "COVIPENDIUM: information available to support the development of medical countermeasures and interventions against COVID-19 " Transdisciplinary Insights 1-267.

This endpoint has been tested in other trials that are listed below.
ϖ An experimental treatment open label control study done between Favipiravir and lopinavir / ritonavir –plus interferon by aerosol inhalation. Shorter viral clearance time was found for the FPV arm versus the control arm (median (interquartile range, IQR), 4 (2.5–9) d versus 11 (8–13) d, $P < 0.001$). Multivariable Cox regression showed that favipiravir was significantly ($p = 0.026$) associated with faster viral clearance, additionally the timing of antiviral therapy reached near significance ($p = 0.055$)

Reference: Cai, M. Yang, D. Liu, J. Chen, D. Shu, J. Xia, et al.Experimental treatment with favipiravir for covid-19: an open-label control study. Engineering (Beijing) (2020), 10.1016/j.eng.2020.03.007)

ϖ A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients

with COVID-19 chose the primary endpoint was viral clearance by day 6. The secondary endpoint was a change in viral load by day 6. Additionally, exploratory endpoints included time to defervescence and resolution of symptoms.

Reference: Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19. Antimicrob Agents Chemother 2020a;(September), doi:http://dx.doi.org/10.1128/AAC.01897-20 AAC.01897-20.

A trial from Russia enrolled 60 patients (40 on favipiravir and 20 on Supportive Care) with primary endpoint as viral elimination. The secondary endpoints were defervescence and RT-PCR negativity.

Reference : Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases. 2021;102:501-8.

ϖ Lately, a phase 3, open-label, randomized, multicenter study (Glenmark Pharmaceuticals) was initiated in India. The primary endpoint was time until the cessation of oral shedding of SARS-CoV-2 virus.
Reference: Singh, P. (2020, April). "A Clinical Study on Favipiravir Compared to Standard Supportive Care in Patients With Mild to Moderate COVID-19." Cochrane COVID-19 Study Register Version 3 from ICTRP (http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43504).

9. I have made a separate comment in the review proforma to say that this manuscript does require separate statistical review.
The study statistician will be happy to answer any required clarifications.
10. Please provide more detail about the placebo. Currently, figure 1 implies that patients will receive 1800mg /800mg of placebo but it is not clear if this is a medication or if not, why there is a dose given.
ϖ Thanks for this, there were an error with giving a dose for placebo. This has been corrected as the placebo does not have a dose.

11. In the discussion the authors list other trials that are testing favipiravir for Covid-19. It would be useful if the discussion included more reflection on their choice of endpoint compared to other trials and why more trials such as theirs are needed in the context of results already published. For example, line 291 states that the study design eliminates bias – can the authors expand on this statement and indicate why their design in particular eliminates bias and which bias they are referring to.
The choice of endpoint has been answered in Q8.
A systemic review and meta-analysis of Favipiravir reported evidence showing potential benefits of this drug in clinical and imaging improvement after treating COVID 19 patients. Therefore there is a need for additional randomized, double-blind clinical trials to form a definite opinion about the rationale to use this drug. There were several drawbacks to the studies that have already been published, such as non-randomized design, small sample sizes, and different durations of treatment, different dosage regimes, and lack of blinding. (1)
Many clinical trials conducted in China, Japan, Russia, and India had an open-label design, which subjects the results to reporting bias. Randomized double-blind placebo control studies (RDPCS) are regarded as the “gold standard” of epidemiologic studies. They are employed to illustrate superiority, equivalence, and non-inferiority. Well-designed RDPCS gives the most robust possible evidence of causation. The benefits of randomization are 1. It avoids selection bias that may happen if either the physician or the patient decides the treatment, 2. It removes most confounding by all known and unknown factors as it prevents an association between the treatment and any other known or unknown factor. Blinding with randomization evades reporting bias as no one is aware of the treatment; hence all treatment groups will be treated the same. The use of placebo as control leads to

the placebo effect where the person on placebo will think that they are taking the actual treatment, which leads them to feel better or respond to it due to wishful thinking. The presence of placebo control will help to compare the drug's effectiveness against the placebo's effectiveness. (2,3,4)
Reference
1.Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. Virol J. 2020 Sep 24;17(1):141. doi: 10.1186/s12985-020-01412-z. PMID: 32972430; PMCID: PMC7512218.
2.William A. 4180 IL route 83, suite 101 Long Groove, IL: Waveland Press, Inc; 9580; Oleckno. Essential epidemiology principles and applications; pp. 147–59
3.Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. 3rd ed. 503 Walnut street, Philadelphia, PA, USA: Williams and Wilkins, a Walters Kluwer business Lippincott; 2007. Designing clinical research; pp. 251–65
4.Manja V, Lakshminrusimha S. Epidemiology and Clinical Research Design, Part 1: Study Types. Neoreviews. 2014 Dec;15(12):e558-e569. DOI: 10.1542/neo.15-12-e558.

12. The authors have used a CONSORT diagram and checklist to summarize the trial protocol but this is usually reserved for when reporting trial recruitment/outcomes. A SPIRIT reporting checklist would be more appropriate to a trial protocol. If all parts of the SPIRIT checklist were addressed, this would fill many of the current gaps in the manuscript. A separate flow diagram for the trial schema could be provided alongside the SPIRIT checklist
We thank the reviewer for this recommendation. We have used now the spirit checklist and added it to our documents.
Minor issues
1. There are several typing errors, for example, the use of capital letters in the middle of sentences; different size fonts in the table, extra commas, lack of full stops (for example line 118). There are several abbreviations that have not been spelled out in full on first use (for example line 238). There are also several abbreviations in the Table. 2. The authors comment that patient and public involvement was "not appropriate". I wonder if they are implying that there was not sufficient time or resources to involve patients in the design of the trial protocol rather than it being inappropriate to do so. 4. Covid-19 is not consistently referenced in the manuscript – for example, COVID19, Covid-19, COVID-19, and COVID 19.
ϖ We thank the reviewer for these observations. We have corrected these inconsistencies in the revised version.
5. Please provide the date the study/protocol was approved by the named ethics committee.
ϖ The date for King Abdullah International Research IRB approval for the first version was 28 April 2020 and for the most recent version is protocol version V2.2 is 25th Nov 2020

6. Line 368 and 373; please provide reference numbers for the review articles cited.
ϖ Done in the manuscript.

7. Statement on line 389 that evidence is misleading. The trial provides high quality
ϖ Thank you for the observation has been corrected. We have modified this statement as "In our study we adopted the design double blind; placebo controlled randomized study which provides best evidence" and added the following reference.
Refrence: Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ. 2000;321(7256):255-6.

Reviewer: 2
Dr. Ashkan Emadi, University of Maryland Baltimore
Comments to the Author:

Major Comments:

1) In the abstract the sample size is 634 (317 per arm), but in the Strengths and Limitations is 576.
ϖ This error has been corrected in the manuscript. The sample size is 576 with 288 subjects per each arm

2) Exclusion criterion #2: how do the investigators establish the presence or absence of "bacterial" pneumonia?
ϖ This will be established through positive sputum cultures. Added to the eligibility criteria.

3) Exclusion criterion #3 & 6: Are patients with previous exposure to favipiravir and without allergy allowed to be enrolled? if not, how does one know about "known" history of hypersensitivity/allergy?
ϖ If Favipiravir was used for COVID 19 in the patient previously he will not be allowed to be enrol in the study.
ϖ Favipiravir is available in Saudi Arabia and approved. But, if patient received it for influenza previously then he can be enrolled if he didn't have allergy to it.

4) Are hospitalized patients excluded? -YES

5) Please define your primary and secondary "objectives" as well as primary and secondary "endpoint(s)".
ϖ This point has been answered in detail for the reviewer 1 .We has added the information to the manuscript from the protocol.

6) I suggest monitoring only the relevant concomitant medications. Monitoring all medications will be huge tasks for the clinical research office and data managers and often it is not necessary.
ϖ Yes, we agree with the reviewer regarding this point.

7) Please clarify who is responsible for the randomization? And who is unblinded to ultimately know which patient receives what?
ϖ Our data management team has developed the randomization scheme through the e-CRF in the Redcap Data base.
ϖ The pharmacist from the clinical trials investigational unit is not part of the study team is unblinded to know which patient receive what treatment.
ϖ We have added the unblinding procedures as an appendix which gives more details to this.

8) Please clarify how placebo is made? And who is making it? Is it centralized in one site and distributed to the other sites?
ϖ The sponsor has imported the placebo from FujiFilm Toyama Chemical Co. and Zhejiang Hisun Pharmaceutical co., Ltd and it is distributed to all other sites by the sponsor as per enrollment of subjects. We have added a table to clarify this.

9) Who is responsible for obtaining the swabs, the clinical team or the research team?
ϖ The swab collection is done by delegated specialist trained clinical personnel part of the research team. This statement has been added in the FOLLOW-UP PERIOD section.

10) How often DSMB will meet? What are the criteria for unblinding the study?
ϖ They will meet at interim analysis after 40% completion of recruitment. The criteria for unblinding have been detailed as an appendix.

11) Please explain the potential causes of false positive and false negative.

False positive tests: The following table provides the sources for the false positive test.
Source Risk
Contamination of samples with amplified nucleic acids (amplicons) High
Carryover contamination of non-amplified nucleic acids from a high-titer specimen or positive controls Moderate
Amplification of nucleic acids from dead/dying organisms Moderate
Nucleic acid contamination of equipment and/or reagents Low
Technical error Low

False negative: The following table provides the sources for the false negative test.
Source Monitoring level

Nucleic acid degradation Controllable
Inhibition of extraction or amplification by inhibitors in specimens Detectable—may or may not be eliminated
Deterioration or decreased efficacy of extraction or amplification Detectable—may be improved
Improper formulation of reagents Detectable—can be avoided
Improper thermal cycling conditions Detectable—can be prevented
Technical errors Avoidable

Refrence: Sefers, S., Z. Pei and Y.-W. Tang (2005). "False positives and false negatives encountered in diagnostic molecular microbiology." Reviews in Medical Microbiology 16(2).

12) It would be very interesting to discuss whether cost/risk-benefit of 2 days improvement in viral clearance in mild cases favorable or clinically meaningful?
ϖ We agree with the reviewer that two-day improvement seems not clinically significant, but such improvement would be significant in a large number of infected patients. Early discontinuation of isolation, decreasing transmissibility, and avoiding hospital visits will have a good impact of the medication at a higher level, especially in areas where high numbers of cases of COVID-19.

Minor comments:
Please change the typescript as below:
1) Title: change "placebo control" to "placebo-controlled"
2) COVID19 should be consistent in the entire typescript. For example, on line 52 & 113 it is "Covid-19" and on line 58 is "COVID19" and on line 62 & 113 it is "COVID-19"
3) several words in the middle of sentences are started with capital letters. Please correct them.
4) On lines 118 & 119 finish the sentences with ".".
5) Inclusion criteria 3 and 4 are redundant

ϖ Thank you for the above comments. These modifications have been done in the manuscript.

Reviewer: 3
Dr. Oriana Nanni, IRST IRCCS
Comments to the Author:

Minor revision/comments:

1. - Page 5 line 152: which concomitant treatment is permitted? Since there is a placebo control group, the definition of concomitant treatments allowed is very important
ϖ None of the investigational antiviral medications for COVID 19 are allowed. Patients will allow

continuing the medications they were already taking prior to the study eg. Antihypertensive or antidiabetics.

2. Pag 5 line 152: It is unclear whether the patient with mild COVID-19 should or can be hospitalized at screening phase and during treatment : if not, how he/she is managed? (Mobile team?)
ϖ The patients with mild COVID-19 are usually not hospitalized and will be seen in COVID-19 dedicated outpatient clinics. Mobile team is an option for our patients who cannot attend some of the clinic visits.
3. Pag 5 line 152: "Male or non-pregnant female " implies that the pregnancy test is mandatory.
ϖ No, testing is not mandatory. Except if the patient requests or is not sure, the study team will provide it.

4. Pag 10 line 271 -275 the: the difference in the definition of ITT and modified ITT is not clear?
The following definition has been added to the manuscript for a clearly understanding and references have been added.
Intention-to-treat:
ϖ ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization
-Modified ITT:
ϖ It is a subset of the ITT that allows the exclusion of some randomized subjects in a justified way such as patients who were deemed ineligible after randomization or patients who withdrew consent or certain patients who never started treatment.

References:
1.Gupta, Sandeep K. “Intention-to-treat concept: A review.” Perspectives in clinical research vol. 2, 3 (2011): 109-12. doi:10.4103/2229-3485.83221

2. Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. Med J Aust. 2003 Oct 20; 179(8):438-40. doi: 10.5694/j.1326-5377.2003.tb05627.x. PMID: 14558871.
5. Based on the emerging evidence, I invite you to pay close attention to the time between the onset of symptoms and the start of therapy. a post-hoc analysis might be useful
ϖ We thank the reviewer for their suggestion and we will definitely consider it.

VERSION 2 – REVIEW

REVIEWER	Hanna, Catherine University of Glasgow, CRUK Clinical Trials Unit
REVIEW RETURNED	02-Feb-2021

GENERAL COMMENTS	This is much improved compared to the previous draft. Thank you for addressing the previous comments. I have a few minor points: - It is still not clear to me if this will be a trial performed in hospital or in the community from this manuscript. One of the exclusion criteria says that patients are excluded if they have moderate/severe disease and are hospitalised. Are patients with mild disease that are hospitalised not excluded? I.e. it is feasible that patients could be recruited when they present to hospital? Or does your definition of mild disease mean that mild disease and hospitalisation are mutually exclusive? - Please update the reference that refers to the number of cases of

	COVID-19 from March 2020 that is in the introduction - this is now out of date. - In the figure "enrolment process" which has been added, the "outcome" tab is not that clear. My understanding is that one of the outcomes was day 15 viral clearance - there is no outcome at day 15 on this diagram.

REVIEWER	Nanni, Oriana IRST IRCCS, Clinical Trial
REVIEW RETURNED	01-Feb-2021

GENERAL COMMENTS	AUTHORS ANSWERED ALL THE QUESTIONS.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Dr. Oriana Nanni, IRST IRCCS
Comments to the Author:
AUTHORS ANSWERED ALL THE QUESTIONS

Reviewer: 1
Dr. Catherine Hanna, University of Glasgow
Comments to the Author:
This is much improved compared to the previous draft. Thank you for addressing the previous comments.
I have a few minor points:
Q1.It is still not clear to me if this will be a trial performed in hospital or in the community from this manuscript. One of the exclusion criteria says that patients are excluded if they have moderate/severe disease and are hospitalised. Are patients with mild disease that are hospitalised not excluded? I.e. it is feasible that patients could be recruited when they present to hospital? Or does your definition of mild disease mean that mild disease and hospitalisation are mutually exclusive?
A1. To assess the patients' eligibility, we only include those with a mild disease from the community. This is mainly due to the setting of the centers in our trial, where we see mild cases in the outpatient clinic. Hospital admission is considered once the patient is critically ill or requiring supplemental oxygen.
If the patient is enrolled with mild disease and later gets hospitalized, the patient may continue the therapy after hospitalization. Yet, we follow the patient as per the protocol to ensure patients safety and assess the outcome.
.
-Q2.Please update the reference that refers to the number of cases of COVID-19 from March 2020 that is in the introduction - this is now out of date.
A2. This was changed to as of 25th Feb 202, 376,000 confirmed cases of the disease were reported. Following reference has been added
Worldometers.info. Totoal Coronavirus Cases in Saudi Arabia [internet]. Dover, Delaware, U.S.A.: Worldometer; 2021 [updated 25 Feb 2021; cited 2021 25 Feb].

-Q3.In the figure "enrolment process" which has been added, the "outcome" tab is not that clear. My understanding is that one of the outcomes was day 15 viral clearance - there is no outcome at day 15 on this diagram.
A3.Thank you for the observation. We have corrected the diagram to reflect the outcome on day 15 in the figure.

VERSION 3 – REVIEW

REVIEWER	Hanna, Catherine University of Glasgow, CRUK Clinical Trials Unit
REVIEW RETURNED	10-Mar-2021

GENERAL COMMENTS	All questions answered - thank you.