Use of Favipiravir for treating patients with COVID-19

RAPID REVIEW

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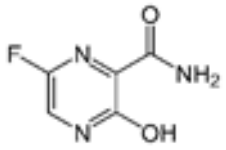
1. CONTEXT AND POLICY ISSUES

In early 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19) as a global pandemic affecting more than 160 countries and regions with at least 350,000 cases and 15,000 deaths worldwide as of 23 March 2020 (Dong, Du & Gardner, 2020). In the Philippines, there were over 3,660 cases of COVID-19 with 163 deaths as of 6 April 2020 (DOH, 2020). The local mortality rate of 4.45% is within the global mortality rate (3%-6%). Note that the rates do not fully account for the asymptomatic cases (Dong, Du & Gardner, 2020; Department of Health, 2020a).

To date, there is no existing treatment targeting SARS-CoV-2. In response to the increasing number of COVID-19 cases, the World Health Organization has announced the SOLIDARITY trial, a global testing of effective treatments across several countries (World Health Organization, 2020a). Furthermore, separate studies and trials using existing drugs in the market have been launched to find a treatment targeting SARS-CoV-2. In the Philippines, the Department of Health endorses the use of The Philippine Society of Microbiology and Infectious Disease (PSMID) treatment guidelines for COVID-19 through its issuance of Department Memorandum No. 2020-0108. The latest PSMID guideline (issued March 31, 2020) has listed several drugs that may be considered for use in hospitalized, probable or confirmed COVID-19 cases with moderate to high-risk pneumonia: off-label use of hydroxychloroquine, chloroquine, lopinavir/ritonavir, and tocilizumab; and, compassionate use of remdesivir. These are all investigational drugs for COVID-19 and do not have high level of evidence, but are based on current limited evidence and expert opinion.

The Health Technology Assessment Council's recommendation was sought to shed light on favipiravir (Avigan®) as potential treatment for COVID-19, in addition to the array of current treatments recommended or being investigated for COVID-19. Favipiravir is a prodrug antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. It was discovered through screening chemical library for antiviral activity against the influenza virus by Fujifilm Toyama Chemical Co., Ltd. (Furuta et. al., 2015).

Table 1. Description of favipiravir	
Synonyms	T-705, Avigan, favilavir
Manufacturer	Fujifilm Toyama Chemical Co., Ltd
Chemical structure	
IUPAC name (chemical name)	6-fluoro-3-hydroxypyrazine-2-carboxamide
ATC Code	J05AX27
Pharmacologic category	Antiviral drug
Available dosage form and strength	200 mg film-coated tablet

Dosing and administration	*For influenza*:* Day 1: 1600 mg twice daily Days 2 through 5: 600 mg twice daily *Administered dose for COVID-19**:* Day 1: 1600 mg, twice a day Day 2-10: 600 mg, twice a day
Mechanism of action	Inside the body, it is converted to its active form, favipiravir-RTP (favipiravir ribofuranosyl-5'-triphosphate) through intracellular phosphoribosylation. It is then recognized as a substrate by RdRp and inhibits the RNA polymerase activity of RNA viruses.

Adverse Reactions, Caution, and Contraindications^	*Adverse reactions (based on frequency):*
	• Less common
	  ○ Increase in blood uric acid
	  ○ Diarrhea
	  ○ Decrease with the number of neutrophils
	  ○ Increase in AST (GOT) levels,
	  ○ Increase of ALT (GPT) levels
	• Frequency unknown
	  ○ Abnormal behavior (serious)
	
	Caution:
	• There is no experience in administration to young children.
	• As there are lots of elderly persons whose physiological functions are deteriorating, administer while observing the conditions of the patient.
	• During the time of delivery of the drug: Make guidance for the PTP packing of the drug to be dosed by taking it out from the PTP sheet
	
	Contraindications:
	Do not administer to pregnant women of women who are possible to be pregnant.

*Note: The following details were adopted from Furuta et. al. (2015), National Center for Biotechnology Information (n.d.), Pharmaceuticals and Medical Devices Agency (2014), *World Health Organization (2020b), **Chen et. al. (2020).*
^The information provided are translated by a certified Japanese-English translator. Product information is the brochure from Fujifilm Toyama Chemical Company (2019) website, the manufacturer of favipiravir (Avigan®).

While it is registered in Japan, it can only be manufactured and distributed at the request of the government for use in the outbreak of a new influenza virus, provided that other influenza antiviral drugs are ineffective or not sufficiently effective, and in whom the efficacy of favipiravir can be expected (Inagaki, 2020; Pharmaceuticals and Medical Devices Agency, 2014). It was also investigated by *Sissoko et. al. (2016)* and *Kerber et. al., (2019)* as a potential agent for Ebola virus during the West Africa Ebola virus outbreak in 2014 but was found to be of no or unclear benefit and is no longer being investigated

(Chertow, Bray, & Palmore, 2020).

To date, there is no conclusive guidance on the use of favipiravir for the treatment of COVID-19; hence, evidence is needed to support its use for such. For this reason, **a rapid review** was conducted to search and synthesize **information on existing COVID-19 treatment guidelines (TGs) or clinical practice guidelines (CPGs)** recommending the use of **favipiravir**, as well as existing **evidence on its clinical efficacy, safety and cost-effectiveness for COVID-19.**

2. POLICY AND RESEARCH QUESTIONS

2.1 Policy question

Should the Philippine government introduce favipiravir as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31?*

2.2 Research questions

1. What are the current country TGs or CPGs which recommend the use of favipiravir in treating patients with COVID-19?

2. What is the clinical efficacy/ effectiveness and safety of favipiravir as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31?*

3. Does favipiravir as an add-on to the DOH-PSMID-recommended treatment regimens represent value for money for the treatment of patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31?*

3. KEY FINDINGS

To date, the World Health Organization (WHO), U.S. Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA) have not listed any medications or vaccines that have been proven to be effective for the treatment or prevention of COVID-19. Furthermore, favipiravir is not included in WHO's multi-country SOLIDARITY trial for COVID-19.

In our review of existing COVID-19 TGs or CPGs across select countries, Japan (as off-label use in its CPG, while clinical trials are ongoing) and Turkey (as compassionate use in its TG) have so far included favipiravir in their guidelines for the treatment of COVID-19 among adults (Tokyo Metropolitan Infectious Disease Surveillance Center, 2020; General Directorate of Public Health, 2020). Meanwhile, its clinical trials on COVID-19 have started in countries such as Italy, Thailand and US through compassionate use, as well as in China and Japan through off-label use as mentioned (Dong, L., Hu, S., & Gao, J., 2020; Aifa Italian Medicines Agency, 2020; Thailand Medical News, 2020; Kongsaengdao, 2020).; Kongsaengdao, 2020).

As with existing evidence on clinical efficacy and safety on the use of favipiravir for COVID-19, the following summarizes the evidence found:

- The first completed trial, an open-label non-randomized controlled trial by *Cai et. al. (2020)* (N=80), compared favipiravir (N=35) with the combination drug lopinavir/ritonavir (N=45). The reported observed outcomes [i.e., faster viral clearance (median: 4 versus 11 days, p<0.001), improvement on chest CT scan imaging after 14 days [91.4% (32/35) versus 62.2% (28/80) of patients, p=0.004], and fewer adverse reactions [11.43% (4/35) versus 55.56% (25/45) of patients, p<0.001] favored favipiravir.
- The second completed trial, an open-label randomized controlled trial by *Chen et. al. (2020)* (N=236), compared favipiravir (N=116) with arbidol (N=120) as add-on therapy to conventional routine therapy. The reported observed outcomes [i.e., clinical recovery rate at day 7 in mild cases [71.43% (70/98) vs 55.86% (62/111) of recovered patients, p=0.02], favored favipiravir. The results, however, for critical COVID-19 cases and COVID-19 patients with hypertension and/or diabetes, show that its benefit is inconclusive. In terms of adverse events, the study noted higher events for raised serum uric acid in the favipiravir versus the control arm. We note, however, that upon the completion of this report, the publisher has withdrawn the paper at the request of the authors.
- While both *Cai et. al. (2020)* and *Chen et. al. (2020)* concluded favorable treatment effect of favipiravir, our critical appraisals show low validity for both studies. Both were exploratory, open-label studies. *Cai et. al. (2020)* was a non-randomized study; and, while *Chen et. al. (2020)* reported performing random sequence generation, there was no mention of allocation concealment. Both studies were therefore assessed to have high risk of selection bias, performance bias and detection bias.
- A rapid review published by Singapore's HTA organization Ministry of Health - Agency for Care Effectiveness (MOH-ACE) which also looked into the same completed trials included in our review noted that further investigation on favipiravir is needed to conclude its efficacy and safety for treating patients with COVID-19.
- As for ongoing clinical trials on favipiravir for COVID-19 treatment, our search detected seven.

No relevant studies were found in terms of its cost-effectiveness. Direct inquiry (Department of Trade and Industry, personal communication, 2020) from the Chinese distributor of Fujifilm Toyama Chemical Co., Ltd. which produces favipiravir (Avigan®) gave a cost of USD 3 or PHP 153.13 per 200-mg tablet (where USD 1 = PHP 51.0440 as per Bangko Sentral ng Pilipinas April 1, 2020 conversion rate). Using the treatment regimen by *Chen et. al. (2020),* the full treatment course (i.e., lasts 10 days) will require a total of 70 tablets per patient amounting to a total treatment cost of PHP 10,719.34 or USD 210 per patient.

Overall, there is limited evidence, to date, to establish the clinical efficacy, safety and value for money of using favipiravir for the treatment of patients with COVID-19. The results of the ongoing trials are anticipated to further conclude the value of favipiravir for COVID-19.

As evidence on the different facets of COVID-19 is ongoing and rapidly evolving, regular scoping for evidence and updating of recommendations are advised.

4. METHODS

4.1 Literature Search Methods

Two reviewers for the clinical and economic evaluation studies, and two reviewers for the TGs or CPGs, as well as economic evaluations performed a limited literature search for relevant studies published from inception to 26 March 2020 via different scientific databases, select HTA agencies, and Google® Search. Evidence pertaining to COVID-19 TGs or CPGs recommending favipiravir were searched through individual country websites as provided and linked by *UpToDate®*. Other TGs or CPGs on favipiravir not included in *UpToDate®* were hand searched via Google® Search.

For clinical efficacy and safety studies, Google Scholar, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov, and LitCovid were used to search for scientific articles. In recognition that this is a potential novel indication for an existing treatment, general searches on Google® Search were also performed to retrieve any relevant scientific or news articles. For economic evaluations, publications on PubMed, LitCovid, Cochrane Library, and of select HTA agencies were reviewed. Search terms used were MeSH terms for nCov-19 and MeSH terms for favipiravir. No filters/restrictions on study type, language and publication date were applied in these databases, except on Google Scholar, where filter on publication date was applied to view publications from year 2019 onwards.

4.2 Selection Criteria and Methods

Two reviewers for the clinical and economic evaluation studies screened the total citations and selected the studies with supervision. The full text of potentially eligible studies with relevant abstracts and titles were retrieved and evaluated for eligibility using the set inclusion and exclusion criteria.

Table 2: Inclusion Criteria	
Population	patients with *confirmed* or *probable* COVID-19 who are referred for treatment
Intervention	favipiravir in combination with supportive treatment (regardless of the dosage form and strength)
Comparator	supportive treatment alone or in combination with other investigational drug/s for COVID-19
Outcomes	Clinical efficacy/ effectiveness: Primary outcomes • Time to viral negativity by RT-PCR, • Time to clinical improvement Secondary outcomes • Incidence of mechanical ventilation by day14, • Incidence of ICU admission by day14, • Time to treatment failure, • All-cause mortality by day14, day28, • The number (proportion) of subjects with viral positive by RT-PCR,

	• Safety assessment according to AE, clinical laboratory examination, ECG and vital signs, etc. Safety: incidence of adverse outcomes Cost-effectiveness: cost per life year saved, cost per case averted, cost per QALY, cost per DALY *(Note: Such as but not limited to the outcome measures listed above)*
Study Designs^	Health technology assessments, systematic reviews (SRs), meta-analyses, TGs, CPGs, primary clinical studies, economic evaluations

Note: Supportive treatment is provision of supplemental oxygen, fluid resuscitation, antipyretics, and/or antimicrobials (except those specified as investigational drugs for COVID-19) for patients with pneumonia and sepsis. This is based on DOH-PSMID recommended guidelines for COVID-19 as of March 31.
^According to American Psychological Association (2002), Treatment Guidelines (TGs) are defined as specific recommendations about treatments to be offered to patients as opposed to practitioner focused, and they tend to be condition or treatment specific. On the other hand, Clinical Practice Guidelines (CPGs) consist of recommendations to professionals concerning their conduct and the issues to be considered in particular areas of clinical practice rather than on patient outcomes or recommendations for specific treatments or specific clinical procedures at the patient level.

Exclusion Criteria
Articles were excluded if they did not meet the selection criteria outlined in Table 2; their full text is not accessible; or they were duplicate publications.

4.3 Data Extraction and Critical Appraisal of included studies

Two reviewers for the clinical efficacy and safety studies, and two reviewers for the TGs, CPGs, and economic evaluations extracted and summarized the key data domains using a standard data extraction tool. Non-English manuscripts or country guidelines included in this review were translated to English language using Google® Translate. The following appraisal tools were intended to be applied to evaluate the overall quality and validity of the included clinical and cost-effectiveness studies:

- Clinical studies: Evaluation of Articles on Therapy tool by *Dans et. al. (2017)*
- Economic evaluations: *Drummond et. al. (1996)* tool

5. SUMMARY OF EVIDENCE

5.1 COVID-19 Guidelines recommending Favipiravir

According to the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA), there are currently no medications or vaccines that have been proven to be effective for the treatment or prevention of COVID-19 to date (WHO, 2020c; CDC, 2020; U.S. FDA, 2020). In the absence of a recognized treatment regimen, several countries, through their Ministries of Health, Infectious Disease Societies, and other relevant agencies, have crafted their own guidelines allowing off-label or compassionate use of certain treatments originally indicated for influenza, SARS, and respiratory viral infections and now being explored for COVID-19.

In our review of existing COVID-19 TGs or CPGs across different countries included (i.e., Australia, Canada, China, Italy, Japan, Russia, Singapore, South Korea, Taiwan, Thailand, Turkey, United Kingdom, and the United States of America), Japan (as off-label use in its CPG, while clinical trials are ongoing) and Turkey (as compassionate use in its TG) have so far included favipiravir in their guidelines for the treatment of COVID-19 among adults (Tokyo Metropolitan Infectious Disease Surveillance Center, 2020; General Directorate of Public Health, 2020). The guidelines are in Japanese and Turkish language respectively; hence, were translated to English language using Google® Translate. Meanwhile, through clinical trial use, favipiravir for COVID-19 was approved in Italy, Thailand, and US under compassionate use, as well as in China and Japan under off-label use (Aifa Italian Medicines Agency, 2020; Thailand Medical News, 2020; Kongsaengdao, 2020; Dong, L., Hu, S., & Gao, J., 2020).

Furthermore, the drug is not included in WHO's multi-country SOLIDARITY trial for COVID-19 as of this writing. This trial, however, has an adaptive design wherein countries have the option to add treatment arms. Currently, China, Japan, Italy, Thailand and US were found to have started separate clinical trials as mentioned above (Dong, L., Hu, S., & Gao, J., 2020; Tokyo Metropolitan Infectious Disease Surveillance Center, 2020; Aifa Italian Medicines Agency, 2020; Kongsaengdao, 2020).

A comparative summary of the status of favipiravir use through country TGs or CPGs and approval for compassionate or off-label use under clinical trial participation can be found in Appendix 1.

5.2 Clinical Efficacy and Safety of Favipiravir

After the search conducted on Google Scholar, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov, LitCovid, and HTA organization websites, a total of 10 studies were included in our review. Our search detected three systematic reviews but these covered all technologies for COVID-19, mentioning favipiravir among others. Hence, we did not include them in the final included studies but were used to detect primary studies on favipiravir which may have not been detected in our total search. We were also able to detect and include an existing rapid review conducted by Singapore MOH-ACE out of the 10 HTA agencies screened (MOH-ACE, 2020). They included some of the trials which were part of our search except for one ongoing trial; hence, this was also included. As such, additional four primary studies were identified from these existing systematic and rapid reviews mentioned. Overall, of the 10 included citations in our review - two were completed trials, one was a rapid review (which included the primary studies included in this review), while the rest are ongoing trials. Appendix 2 contains the PRISMA flow selection diagram of studies.

5.2.1 General Study Characteristics

5.2.1.1 Completed trials/ studies

Both studies were open label trials - one [i.e., *Cai et. al. (2020)*] non-randomized and one [i.e., *Chen et. al. (2020)*] randomized. In terms of population, *Cai et. al. 2020* (N=80; intervention group = 35 versus control group = 45) included COVID-19 confirmed cases only (ie, confirmed by RT-PCR) while *Chen et. al. (2020)* (N=236; intervention group = 116 versus control group = 120) included patients with COVID-19 pneumonia where about half were detected to have negative nucleic acid tests at screening but were still included in the study on the basis of their clinical diagnosis and CT results. The investigators explained that patients with contact

history, typical CT imaging results of COVID-19 and obvious clinical symptoms who had negative nucleic acid test could be related to the previous treatment, onset time, sampling and detection kit. There was no difference in the provided favipiravir regimen in the studies. As with comparators, Lopinavir/ ritonavir was the comparator for *Cai et. al. (2020);* while Arbidol was the comparator for *Chen et. al. (2020)*. Finally, for the outcomes, the primary clinical efficacy outcome was time of viral clearance and improvement of chest CT scan for *Cai et. al. (2020)*; and, clinical recovery rate at day 7 for *Chen et. al. (2020).* We note, however, that upon the completion of this report, the publisher has withdrawn the manuscript of *Cai et. al. (2020)* at the request of the authors. The study characteristics are tabulated on Appendix 3.

5.2.1.2 Ongoing trials/ studies

Of the seven ongoing trials (see Table 3), two are still in the recruitment stage. Generally, these trials are comparing the efficacy and safety of favipiravir with other investigational treatments for COVID-19.

Table 3. Ongoing trials on treatments for COVID-19

Trial registration Number	Investigator	Title of the study
ChiCTR2000029544	Qiu, Y. 2020a	A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients who are still positive on virus detection under the current antiviral therapy
ChiCTR2000029600	Liu, Y. 2020	Clinical study for safety and efficacy of Favipiravir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)
ChiCTR2000029548	Qiu, Y. 2020b	Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients
2020GH0006YJ	Sihuan Pharmaceutical Holdings Group Ltd	*Study title not indicated, but compares high, middle and low dosage of favipiravir. It is a randomized, multicenter trial.*
NCT04319900	Liu, L., Beijing Chao	Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia

(Recruiting)	Yang Hospital	
NCT04310228 (Recruiting)	Wang, G., Peking University First Hospital	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019
NCT04303299 (Not yet recruiting)	Kongsaengdao, S., Rajavithi Hospital	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19 : A Randomized Control Trial (THDMS-COVID19)

5.2.1.3 Evidence synthesis from HTA agencies

The rapid review by Singapore MOH-ACE included two completed studies [i.e., *Cai et. al. (2020)*; *Chen et. al. (2020)*] and three on-going trials [i.e., *Wang (2020), Kongsaengdao (2020), Sihuan Pharmaceutical Holdings Group Ltd (2020)*]. As mentioned, all of these trials were part of the included studies in our review.

5.2.2 Summary of Findings

5.2.2.1 Completed trials/ studies

Cai et. al. (2020), (N=80; intervention group = 35 versus control group = 45)

- **Time of Viral Clearance:** The median time of viral clearance for the patients treated with favipiravir was estimated to be 4 days which was significantly shorter than the time for patients in the control group which was 11 days.
- **Chest CT Changes:** Favipiravir appears to be more beneficial than lopinavir/ritonavir for patients who tested positive for COVID-19 after 14 days of follow-up post-treatment.
- **Antiviral-associated outcomes:** The total number of adverse reactions in the favipiravir arm of the study was four (11.43%), which was significantly fewer than the 25 adverse reactions (55.56%) in the control arm ($P < 0.001$).
- **Conclusion**: In this open-label non randomized control study, favipiravir showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection.

Chen et. al. (2020), (N=236; intervention group = 116 versus control group = 120)

- **Clinical Recovery at Day 7:** Favipiravir was more beneficial among mild cases compared to arbidol, but inconclusive among critical cases and patients with hypertension and

diabetes. For mild patients, recovery rate was 55.86% (62/111) in the arbidol group and 71.43% (70/98) in the favipiravir group (P = 0.0199). For critical patients, recovery rate was 0 (0/9) in the arbidol group and 5.56% (1/18) in the favipiravir group (P =0.4712). For COVID-19 patients with hypertension and/or diabetes, rate was 51.43% (18/35) in the arbidol group and 54.76% (23/42) in the favipiravir group (P = 0.7704).

Need for auxiliary oxygen therapy or non-invasive mechanical ventilation: No statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate between 2 groups (both P > 0.05)

- **Antiviral-associated adverse events (AEs):** 37 AEs in the favipiravir group and 28 cases in the arbidol group were observed. The most common AE was raised serum uric acid versus vs,], more common in patients of the favipiravir group [16/116, (13.79%)] than those in the arbidol group [3/120, (2.50 %)] (P = 0.0014).
- **Conclusion**: In ordinary COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment because of the higher 7 day's clinical recovery rate and more effectively reduced incidence of fever, cough except some antiviral-associated adverse effects.

5.2.2.2 Evidence synthesis from HTA agencies

Singapore MOH-ACE detected two completed trials and three ongoing trials. They reported that no international professional bodies recommend the use of favipiravir for the treatment of COVID-19. As such, they recommended the need for further investigation to conclude its efficacy and safety for treating patients with COVID-19. They likewise noted the results of the three ongoing trials that will determine whether favipiravir should be used more widely in their setting.

5.2.3 Summary of Critical Appraisal (Completed trials/studies)

While both *Cai et. al. (2020)* and *Chen et. al. (2020)* concluded favorable treatment effect of favipiravir, our critical appraisals show low internal validity for both studies. Both were exploratory, open-label studies. Further, *Cai et. al. (2020)* was a non-randomized study; and, while *Chen et. al. (2020)* reported performing random sequence generation, there was no mention of allocation concealment. Hence, there was high risk of selection bias, performance bias and detection bias in both studies. The details of the critical appraisal for the two papers can be seen on Appendix 4.

5.3 Cost-effectiveness of favipiravir

Literature search from PubMed, LitCovid, Cochrane, and select HTA agencies yielded no existing evidence on the cost-effectiveness of favipiravir (see Appendix 2); therefore, no evidence summary to support its cost-effectiveness can be provided to establish its recommendation.

In the absence of CEA, we also searched for the available commercial price of favipiravir (Avigan®). However, the search did not yield much information except through direct inquiry (Department of Trade and Industry, personal communication, 2020) from the Chinese distributor of Fujifilm Toyama Chemical Co., Ltd. which produces favipiravir (Avigan®) gave a cost of USD 3 or PHP 153.13 per 200-mg

tablet (where USD 1 = PHP 51.0440 as per Bangko Sentral ng Pilipinas April 1, 2020 conversion rate). Using the treatment regimen by *Chen et. al. (2020),* the full treatment course (i.e., lasts 10 days) will require a total of 70 tablets – 16 tablets for Day 1 then 6 tablets per day for Days 2-10 – per patient amounting to a total treatment cost of PHP 10,719.34 or USD 210 per patient. In comparison, Table 4 shows the treatment cost of other COVID -19 investigational drugs in the latest DOH-PSMID guidelines.

Table 4. Comparative costs of DOH-PSMID-recommended COVID-19 investigational drugs (as of 31 March 2020) **per treatment course per person**

Drug	Unit cost	Dosing Regimen based on PSMID guidelines (31 March 2020)	Total cost per treatment course per person
Hydroxychloroquine (200 mg tablet as sulfate)	Php 55 - 62.75 per tablet *(source: DOH Drug Price Watch website, 2020)*	*200mg 2 tabs BID day 1 then 1 tab BID x 9 days*	Php 1,210.00 - Php 1,380.50
Chloroquine (250 mg tablet as phosphate or diphosphate)	Php 70 per tablet *(source: DOH Supplemental Project Procurement Plan 2020)*	*500mg BID x 10 days*	Php 2,800.00
Lopinavir + ritonavir 200mg / 50 mg	Php 15 per tablet *(source: DOH Supplemental Project Procurement Plan 2020)*	*200/50mg 2 tabs BID PO x 14 days*	Php 840.00
Tocilizumab 200mg/10mL vial 400mg/20mL vial	PHP 40,000.00 per 400mg/20mL vial *(source: DOH Supplemental Project Procurement Plan 2020)*	4-8mg/kg single dose with recommended dose of 400mg IV diluted in 0.9 NS to 100mL, given as a 2-hour infusion A single extra dose may be given after 12 hours at the discretion of the provider	Php 40,000.00
Remdesivir	No cost data available	200 mg IV loading dose (infused over 30 min) on Day 1 followed by 100 mg once daily IV (infused over 30 min) maintenance dose = Recommended remdesivir dosing duration is a total of 10 days, but dosing may be continued for an additional 4 days at 100 mg IV once daily if COVID-19 remains detectable at day 10 of treatment.	Cannot be computed

6. LIMITATIONS

This review recognizes the following limitations: First, as this is a rapid review, certain steps of a systematic review were abbreviated and the search included published studies only. The possibility of missing unpublished evidence still remains. Second, the translations of the Turkish and Japanese guidelines were not translated by a professional translator. We reckon, however, that they are unlikely to be inaccurately translated since favipiravir was mentioned in the Turkish guidelines in English text, while the Japanese guideline section on Favipiravir was validated using another translator application Microsoft Translator. Lastly, as evidence on the different facets of COVID-19 is ongoing and rapidly evolving, the evidence presented here can rapidly change as well.

7. CONCLUSION

In summary, our rapid review found two countries so far which have included favipiravir for the treatment of COVID-19 - Japan (as off-label use in its CPG, while clinical trials are ongoing) and Turkey (as compassionate use in its TG). Meanwhile, through clinical trial use, favipiravir for COVID-19 was approved in Italy, Thailand, and the United States of America under compassionate use, as well as in China and Japan under off-label use.

As for the clinical efficacy and safety of favipiravir, there were two completed clinical trials on favipiravir by *Cai et. al. (2020)* and *Chen et. al. (2020*). While the results of both trials clinically favored favipiravir, our critical appraisals show that both studies have low internal validity because of high risk of selection bias, performance bias and detection bias. Currently, there are seven ongoing trials for favipiravir in several countries, and the results of these trials are anticipated to establish further evidence on its relative treatment effect and will determine the recommendation on its use for COVID-19 treatment.

At a unit cost of USD 3 or PHP 153.13 per 200-mg tablet of favipiravir (Avigan®), the total cost per treatment course per patient was estimated at PHP 10,719.34 or USD 210.

Finally, as evidence on the different facets of COVID 19 is ongoing and rapidly evolving, regular scoping for evidence and updating of recommendations are strongly advised.

8. DECLARATION OF CONFLICT OF INTERESTS

The reviewers have no relevant affiliations or financial involvement with any organization or entity with a financial interest or in financial conflict with the subject matter or materials discussed in the review report.

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APPENDIX

Appendix 1. COVID-19 Treatment Guideline Recommendations on Favipiravir

Country / Organization	Is favipiravir registered? (Indication if possible)	Is there off-label use* or compassionate use** of Favipiravir for COVID-19 in the country?	Is Favipiravir recommended in the COVID-19 TGs or CPGs in the country?	Other medications used in the management	References
WHO	Not applicable	Not applicable	No	No antivirals recommended currently Investigational: ● Remdesivir ● Chloroquine and Hydroxychloroquine ● Ritonavir/ Lopinavir ● Ritonavir/ Lopinavir and Interferon-beta	World Health Organization. (2020c). *Clinical management of severe acute respiratory infection (SARI) whenCOVID-19 disease is suspected*. Retrieved 25 March 2020 from https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected Kupferschmidt, K & Cohen, J. (2020). *WHO launches global megatrial of the four most promising coronavirus treatments*. Retrieved 25 March 2020 from https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments
Australia	No	No	No	Off-label use: ● Lopinavir / Ritonavir +/- Hydroxychloroquine Investigational: ● REMAP-CAP: ICU patients. Arms: Lopinavir / Ritonavir, Hydroxychloroquine,	New South Wales Ministry of Health. (2020). *Interim Guidance on use of antiviral therapy in COVID-19*. Retrieved 25 March 2020 from https://www.health.nsw.gov.au/Infectious/diseases/Pages/covid-19-antiviral-therapy-interim-guidance.aspx

				both or none ● ASID: ward patients. Arms: Lopinavir / Ritonavir, Hydroxychloroquine, both or none	
Canada	No	No	No	● Remdesivir (patient to patient basis) Investigational ● Colchicine (COLCORONA trial)	Canada Ministry of Health. (2020). *Coronavirus disease (COVID-19): For health professionals.* Retrieved last 25 March 2020 from https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals.html
China	Yes, for Influenza	Yes (off-label)	No	● Interferon-alpha ● Lopinavir/Ritonavir ● Arbidol ● Ribavirin ● Chloroquine phosphate ● Tocilizumab ● Corticosteroids	China National Health Commission. (2020). *Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (7th ed.)* Retrieved last March 25, 2020, from http://kjfy.meetingchina.org/msite/news/show/cn/3337.html Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug discoveries & therapeutics, 14(1), 58–60. https://doi.org/10.5582/ddt.2020.01012 陈子琰 . (n.d.). Potential coronavirus drug approved for marketing. Retrieved from https://www.chinadaily.com.cn/a/202002/17/WS5e49efc2a310128217277fa3.html
China - Zhejiang Univ.	Yes, for Influenza	Yes (off-label)	No	● Lopinavir/Ritonavir ● Arbidol	First Affiliated Hospital, University of Zhejiang University, School of Medicine. (2020). Handbook of

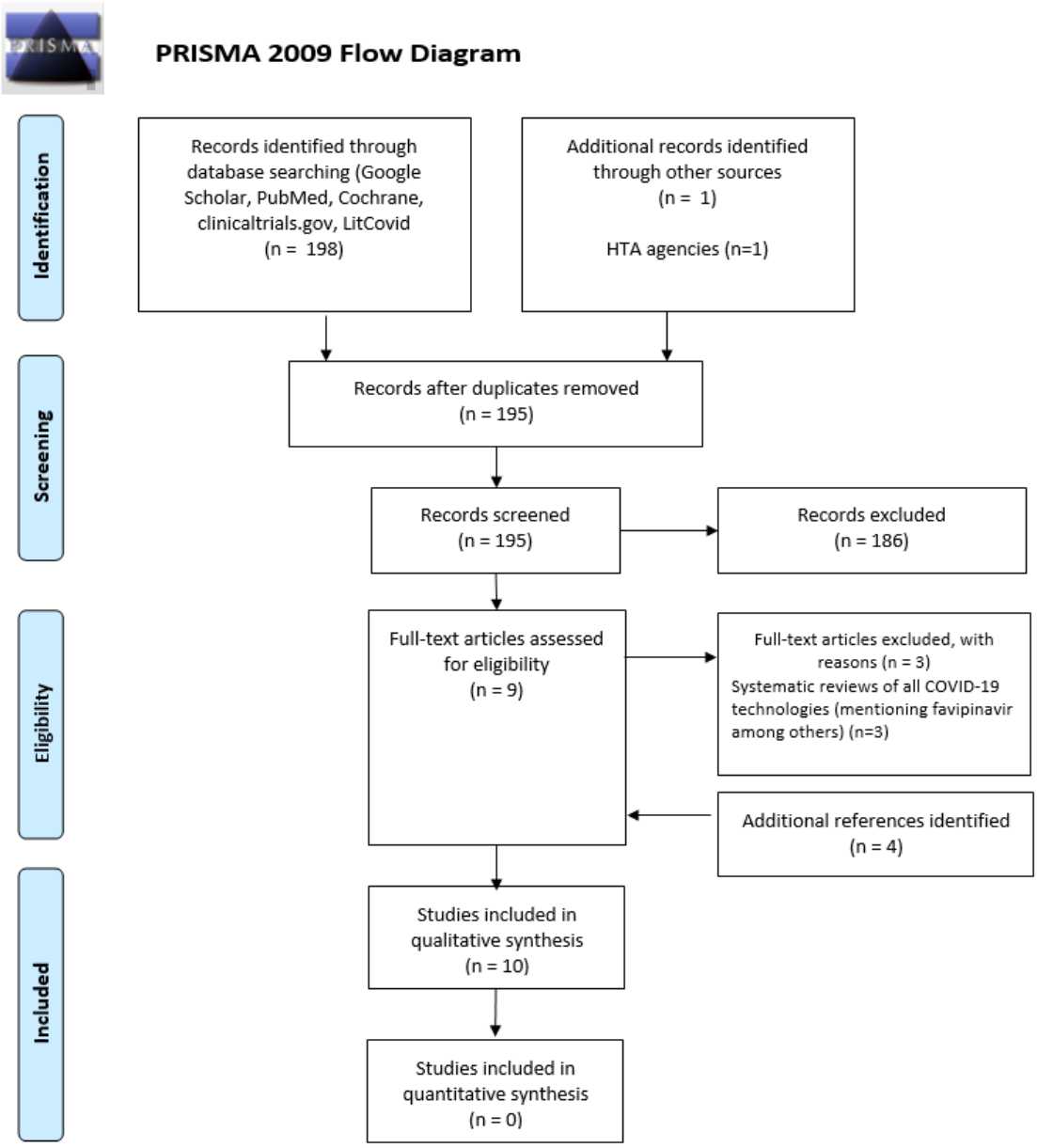
School of Medicine				• Nebulized Interferon • Darunavir/ Cobicistat • Chloroquine • Corticosteroids	COVID-19 Prevention and treatment. Retrieved March 25 2020 from https://covid-19.alibabacloud.com/
Italy	No	Yes (compassionate)	No	Investigational: • Lopinavir/ Ritonavir	Aifa Italian Medicines Agency. (2020). *Favipiravir: Update of the evaluation of the CTS.* Retrieved last 26 March 2020 from https://www.aifa.gov.it/web/guest/-/favipiravir-aggiornamento-della-valutazione-della-ctsahh
Japan	Yes, for the treatment of novel or re-emerging pandemic influenza virus infections	Yes (off-label)	Yes, recommended in their CPG	Listed in Concept of treatment with antiviral drugs for COVID-19: • Lopinavir and Ritonavir • Ciclesonide	Tokyo Metropolitan Infectious Disease Surveillance Center. (2020). Guide to the treatment of new coronavirus infectious diseases (first edition). Retrieved March 25 2020 from http://idsc.tokyo-eiken.go.jp/assets/diseases/respiratory/ncov/treatmentguid.pdf Bryner, J. (2020). *Flu drug used in Japan shows promise in treating COVID-19*. Retrieved last March 25 2020 from https://www.livescience.com/flu-drug-could-treat-coronavirus.html
Russia	No	No	No	No specific recommendation on anti-virals • Ribavirin • Lopinavir/ Ritonavir • Combined with empirical antibiotics for pneumonia • Aprotinin • Glucocorticoids	Russia Ministry of Health. (2020). *Temporary Guidelines for the prevention, diagnosis, and treatment of the new 2019-coronavirus infection*. Retrieved 25 March 2020 from https://www.rosminzdrav.ru/news/2020/01/30/13236-vremennye-metodicheskie-rekomendatsii-po-profilaktike-diagnostike-i-lecheniyu-novoy-koronavirusnoy-infektsii-2019-ncov Biomedservice. (2001). *Cyclopheron 12.5% 2 mL. No. 5 RR D/ V/ M AMP./ polysan.* Retrieved 25 March 2020 from http://www.biomedservice.ru/price/goods/1/1132

Singapore	No	No	No	Investigational: ● Remdesivir ● Lopinavir and Ritonavir ● Chloroquine	Ministry of Health Singapore. (2020). *Should favipiravir be used for COVID-19?* Retrieved last 26 March 2020 from https://www.moh.gov.sg/docs/librariesprovider5/clinical-evidence-summaries/favipiravir-for-covid-19-(26-march-2020).pdf Saw Swee Hock School of Public Health. (2020). COVID-19 Science Report: Therapeutics. Retrieved 25 March 2020 from https://sph.nus.edu.sg/wp-content/uploads/2020/03/COVID-19-Science-Report-Therapeutics-23-Mar.pdf
South Korea	No	No	No	Investigational: ● Lopinavir/ Ritonavir ● Chloroquine or Hydroxychloroquine ● Ribavirin ● Interferon-alpha	Physicians work out treatment guidelines for coronavirus. (2020, February 13). Retrieved from http://www.koreabiomed.com/news/articleView.html?idxno=7428
Taiwan	No	No	No	Investigational: ● Remdesivir	Taiwan Centers for Disease Control. (2020). *Coronavirus disease 2019 (COVID-19).* Retrieved last March 25 2020 from https://www.cdc.gov.tw/En/Category/ListContent/bg0g_VU_Ysrgkes_KRUDgQ?uaid=0nAzwpXdBNIAPOvJhwrGoQ
Thailand	No	Yes (compassionate)	No	Investigational (through WHO's Solidarity Trial): ● Remedesivir ● Lopinavir and Ritonavir ● Lopinavir and Ritonavir plus Interferon beta	Kongsaengdao. (2020). *Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19 : A Randomized Control Trial (THDMS-COVID19).* Retrieved last 26 March 2020 from https://clinicaltrials.gov/ct2/show/NCT04303299?term=favipiravir&draw=3&rank=12

				● Chloroquine	World Health Organization Thailand. (2020). Coronavirus disease 2019 (COVID-19) WHO Thailand Situation Report – 23 March 2020. Retrieved 25 March 2020 from https://www.who.int/docs/default-source/searo/thailand/2020-03-23-tha-sitrep-30-covid19-final.pdf?sfvrsn=6d9f54f4_0
Turkey	No	Yes (compassionate)	Yes, recommended in their TG	Investigational: ● Oseltamivir ● Lopinavir/ Ritonavir	General Directorate of Public Health. (2020). *Adult patient treatment and management.* Retrieved last 6 April 2020 from https://covid19bilgi.saglik.gov.tr/depo/tedavi/COVID19_Eriskin_Hasta_Tedavisi_02042020.pdf
United Kingdom	No	No	No	Investigational: ● Lopinavir / Ritonavir and dexamethasone	NHS Clinical Management of COVID-19. (2020). Last accessed on March 25 2020 https://www.england.nhs.uk/coronavirus/secondary-care/management-confirmed-coronavirus-covid-19/clinical-medical-management/ Rigby, S. (2020, March 24). Coronavirus: UK patients to test existing drugs as COVID-19 treatments. Retrieved from https://www.sciencefocus.com/news/coronavirus-uk-patients-to-test-existing-drugs-as-covid-19-treatments/
United States	No	Yes (compassionate)	No	Investigational: ● Remdesivir	United States Centers for Disease Control and Prevention. (2020). *Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19).* Retrieved March 25, 2020, from https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

** An off-label refers to the use of a licensed medicinal product prescribed for an indication, or to a patient for which the product is not specifically licensed*
*** A compassionate use refers to the use of the medicinal product not licensed and not used as a treatment for any disease*

Appendix 2. PRISMA Flow Diagram of included studies (Clinical Efficacy and Safety of favipiravir)



Appendix 3. Description of Studies for Clinical Efficacy and Safety of favipiravir

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
Completed trials					
Cai, et al., (2020) Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study (Upon the completion of this report, the publisher has withdrawn the paper at the request of the authors)	open-label, nonrandomized controlled trial	China	P: Patients with laboratory confirmed COVID-19 (N = 80) I: FPV + IFN-alpha 1b (N = 35) C: LPV/RTV + IFN-alpha 1b (N = 45) O: time of viral clearance, chest CT improvement	Time of viral clearance: FPV: 4 days (2.5 - 9 days) LPV/RTV: 11 days (8 - 13 days) Chest CT improvement: FPV: 91.4% (32/35) LPV/RTV: 62.2% (28/45) (P = 0.004) *Improvement only evident on day 14* *It is also important to note that the study stated that the number of adverse reactions was significantly fewer in favipiravir (11.43%, 4/35 patients) compared to the lopinavir/ritonavir (55.56%, 25/45 patients) (p<0.001).*	https://doi.org/10.1016/j.eng.2020.03.007
Chen, et al., (2020) Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial	open-label randomized controlled trial	China	P: Patients with confirmed COVID-19 (N = 236) I: FPV + favipiravir (N = 116) C: Arbidol + routine therapy (N = 120) O: Clinical recovery rate after 7 days	Clinical recovery rate: Ordinary/ Mild Patients: FPV: 71.43% (70/98) recovery Arbidol: 55.86% (62/111) recovery (P = 0.0199) Patients with HTN or Diabetes: FPV: 54.76% (23/42)	https://doi.org/10.1101/2020.03.17.20037432

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
				Arbidol: 51.43% (18/35) (P = 0.7704) Conclusion: FPV is beneficial in terms of clinical recovery at day 7 among patients with no hypertension and/or diabetes *Secondary outcomes for ordinary patients have shown that time of cough relief and fever duration is significantly shorter in favipiravir (p<0.001 for both outcomes)*	
Ongoing trials					
Qiu, Y. (2020a) A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients who are still positive on virus detection under the	rando mized control led trial	China	P: 18 to 75 years of age, male or female who tested positive for novel coronavirus infection after the onset of symptoms using a real time polymerase chain reaction (RT-PCR)-based diagnostic assay; I: current antiviral treatment PLUS Baloxavir Marboxil tablets OR favipiravir tablets C: current antiviral treatment O: Primary – • Time to viral negativity by RT-PCR, • Time to clinical improvement	N/A	http://www.chictr.org.cn/com/25/hvshowproject.aspx?id=21995

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
current antiviral therapy			Secondary – • Incidence of mechanical ventilation by day14, • Incidence of ICU admission by day14, • Time to treatment failure, • All-cause mortality by day14, day28, • The number (proportion) of subjects with viral positive by RT-PCR, • Safety assessment according to AE, clinical laboratory examination, ECG and vital signs, etc.		
Liu, Y. (2020) Clinical study for safety and efficacy of Favipiravir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	*No information*	China	P: *No information* I: *No information* C: *No information* O: *No information*	N/A	*No information*
Qiu, Y. (2020b) Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus	Randomized, open-label, controlled trial	China	P: Aged 18 to 75 years male or female, tested positive for novel coronavirus infection after the onset of symptoms using a real time polymerase chain reaction (RT-PCR)-based diagnostic assay I: Baloxavir Marboxil OR Favipiravir OR Lopinavir-Ritonavir C: *not specified* O: Primary – • Time to viral negativity by RT-PCR, • Time to clinical improvement: Time from start of study drug to hospital discharge or to NEWS2<2 for 24 hours.	N/A	http://www.chictr.org.cn/showprojen.aspx?proj=49015

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
pneumonia, NCP) patients			Secondary – • Incidence of mechanical ventilation by day7, day14, • Incidence of ICU admission by day7, day14, • Time to treatment failure, determined as death, mechanical ventilation or ICU admission • All-cause mortality by day14, day28 • Incidence of complications • Incidence and duration of antibiotic treatment • The number (proportion) of subjects with viral positive by RT-PCR by day7, day14 • Safety assessment according to AE, clinical laboratory examination, ECG and vital signs, etc.		
Liu, L. (2020). Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia	Clinical trial	China	P: Patients previously diagnosed with novel coronavirus pneumonia I: favipiravir tablets + chloroquine phosphate tablets tablets; favipiravir tablets C: placebo O: Time of improvement or recovery of respiratory symptoms; Number of days from positive to negative for test of swab or sputum virus nucleic acid; Frequency of improvement or recovery of respiratory symptoms	N/A	https://clinicaltrials.gov/ct2/show/NCT04319900?term=favipiravir&cond=coronavirus&draw=2&rank=1
Wang, G. (2020). Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	Clinical trial	China	P: Clinically diagnosed with Corona Virus Disease 2019 I: Favipiravir Combined With Tocilizumab C: Favipiravir; Tocilizumab O: Clinical cure rate [Time Frame: 3 months]	N/A	https://clinicaltrials.gov/ct2/show/NCT04310228?term=favipiravir&cond=

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
					coronavirus&draw=2&rank=2
Kongsaengdao, S. (2020) .Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19 : A Randomized Control Trial (THDMS-COVID19)	Clinical trial	Thailand	P: diagnosed to be COVID19 I: Oseltamivir plus Chloroquine in Mild COVID19; Darunavir and Ritonavir plus oseltamivir; Lopinavir and Ritonavir plus Oseltamivir in mild COVID19; Lopinavir and Ritonavir Oseltamivir moderate to severe COVID19; Favipiravir lopinavir /Ritonavir for mod. to severe; Darunavir /ritonavir oseltamivir chloroquine mod-severe; Darunavir /ritonavir favipiravir chloroquine mod-severe C: Conventional Quarantine O: SARS-CoV-2 eradication time [Time Frame: Up to 24 weeks] Eradication of nasopharyngeal SARS-CoV-2	N/A	https://clinicaltrials.gov/ct2/show/NCT04303299?term=favipiravir&cond=coronavirus&draw=2&rank=3

Characteristics of excluded studies (Clinical efficacy and safety of favipiravir)

Author, Year	Reason for exclusion
Prajapat, et. al (2020)	Systematic review covering all technologies for COVID-19, mentioning favipiravir among others.
Qiu, R. et. al. (2020)	Systematic review covering all technologies for COVID-19, mentioning favipiravir among others.
Zhu et. al. (2020)	Systematic review covering all technologies for COVID-19, mentioning favipiravir among others.

Appendix 4. Critical Appraisal of Two Completed Trials

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

Author: Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., … Liu, L. (2020)

Critical Appraisal

Reference: https://www.sciencedirect.com/science/article/pii/S2095809920300631

1. DIRECTNESS

Research Question	
P	Patients aged 16-75 years old with laboratory-confirmed COVID-19, detected by the real-time quantitative polymerase chain reaction (qPCR) method admitted in The Third People's Hospital in Shenzhen (N = 80) *"All patients admitted to both the FPV and the control arms of the study were assessed for eligibility criteria. The inclusion criteria included: aged 16–75 years old; respiratory or blood samples tested positive for the novel coronavirus; duration from disease onset to enrolment was less than 7 days; willing to take contraception during the study and within 7 days after treatment; and no difficulty in swallowing the pills."* *"The presence of SARS-CoV-2 was detected by the real-time quantitative polymerase chain reaction (qPCR) method, as previously reported"* Page 2 Paragraph 5
I	Oral favipiravir (FPV) (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) plus interferon (IFN)-alpha 1b aerosol inhalation (5 million U twice daily), (N = 35) Course of treatment: 14 days *"FPV (Haizheng Pharmaceutical Co., 200 mg per tablet) was given orally. The dose was 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14.* *In addition, all participants received IFN-a1b 60 micrograms (Beijing Tri-Prime Gene Pharmaceutical Co., 30 micrograms per ampule) twice daily by aerosol inhalation."* *Page 2 Paragraph 6*
C	Lopinavir (LPV)/ritonavir (RTV), (Days 1–14: 400 mg/100 mg twice daily) plus IFN-alpha 1b aerosol inhalation (5 million U twice daily), (N = 45) *"LPV/RTV (AbbVie Inc., 200 mg/50 mg per tablet) were given orally. The dose was LPV 400 mg/RTV 100 mg twice daily. Both FPV and LPV/RTV were continued until the viral clearance was confirmed or until 14 days had passed. In addition, all participants received IFN-alpha 1b 60 mg (Beijing Tri-Prime Gene Pharmaceutical Co., 30 lg per ampule) twice daily by aerosol inhalation."* Participants: 45 patients Course of treatment: 14 days *Page 2 Paragraph 6*

O	Primary outcomes: time of viral clearance and improvement of chest CT scan Time of viral clearance *"Viral clearance was defined as the presence of two consecutive negative results with qPCR detection over an interval of 24 hours."* Improvement rate of chest computed tomography (CT) scans on Day 14 after treatment *"Chest CT scans were conducted on Days 4, 9, and 14 after treatment, with a fluctuate of 2 days. The CT findings were graded and scored by two medical diagnostic radiographers who were blind to grouping. The CT findings were graded on a three-point scale: 1 as normal attenuation, 2 as ground-glass attenuation, and 3 as consolidation. Each lung zone—with a total of six lung zones in each patient—was assigned a score on the following scale, according to the distribution of the affected lung parenchyma, using]: 0 as normal, 1 as 25% abnormality, 2 as 25%–50% abnormality, 3 as 50%–75% abnormality, and 4 as 75%abnormality. The four-point scale of the lung parenchyma distribution was then multiplied by the radiologic scale described above. Points from all zones were added for a final total cumulative score, with a value ranging from 0 to 72. A change of ''Improve" inthe chest CT was defined as the total cumulative score being lower than before medication; a change of ''Worse" was defined as the total cumulative score being higher than before medication; anda change of ''Constant" was defined as the total cumulative score being the same as before treatment."* *Page 2 Paragraph 7 and 8* Safety outcomes: Adverse reactions included diarrhea, nausea, vomiting, rash, liver and kidney injury, others *"Safety was assessed by a standardized questionnaire for adverse events and by laboratory tests."* *Page 3 Paragraph 1, Page 6 Table 5*

2. APPRAISAL OF VALIDITY

2.1. Were the patients randomly assigned to treatment groups? (Randomization)

No

"For the specific epidemic situation of COVID-19, we chose to conduct an open-label nonrandomized control study in the isolation ward of the national clinical research center for infectious diseases (The Third People's Hospital of Shenzhen), Shenzhen, China."

Page 2 Paragraph 4

Based on the patient flow diagram, patients were assigned to treatment or control arm based on the date of their enrollment in the study. Patients who satisfied the screening criteria from January 24 to January 30, 2020 were assigned to the control arm. Patients who satisfied the screening criteria from January 30 to February 14, 2020 were assigned to the treatment arm.

Page 3 Figure 2

2.2. Was allocation concealed? (Allocation Concealment)

Not mentioned

2.3. Were baseline characteristics similar at the start of the trial?

No, although at a glance, there might be no difference based on statistical non-significance; but numerically, there are more patients who were male (i.e., FPV = 14/35 vs LPV/RTV = 21/45), aged 65 years and older (i.e., FPV = 4/35 vs LPV/RTV = 7/45), and presented fever symptoms (i.e., FPV = 22/35 vs LPV/RTV = 37/45) in the control arm.
Page 4 Table 1

2.4. Were patients blinded to treatment assignment?

No
This is an open-label study where both patients and researchers were not blinded in terms of treatment assignment.

2.5. Were caregivers blinded to treatment assignments?

No
In this study, researchers did not explicitly mention blinding of caregivers but it can be implicit in the screening of patients and the study design being an open-label study.

2.6. Were outcome assessors blinded to treatment assignment?

No.
Blinding was only performed for chest CT. There was no mention of blinding for the assessment of other outcomes.
"The CT findings were graded and scored using the method described previously by two medical diagnostic radiographers who were blind to grouping."
Page 2 Paragraph 7

2.7. Were all patients analysed in the groups to which they were originally randomized?

No
Not all analysis included the original assigned patients. The multivariate analysis of the changes in chest CT particularly for Day 9 after treatment missed the inclusion of 3 patients in the treatment group. The reason behind was not mentioned.

2.8. Was follow-up rate adequate?

Yes
All patients assigned to each group are accounted for with their outcomes noted. There are no patient drop-outs.
Page 3 Paragraph 3

3. APPRAISING THE RESULTS

3.1. How large is the effect treatment?

The outcomes were originally analyzed using multivariate analysis of viral clearance and multivariate analysis for the changes in chest CT. As data were provided in the paper, we are able to calculate for comparative values in selected outcomes.

Primary Outcome: Time of Viral Clearance

"The median time of viral clearance for the patients treated with FPV, designated as Group A, was estimated to be 4 d (IQR: 2.5–9), which was significantly shorter than the time for patients in the control group, designed as Group B, which was 11 d (IQR: 8–13) ($P < 0.001$)."

Primary Outcome: Chest CT Changes

Favipiravir appears to be more beneficial than lopinavir/ritonavir for patients who tested positive for COVID-19 after 14 days of follow-up post-treatment. However, no statistically significant difference was observed between the experimental and control group at days 4 and 9 after treatment.
Based on Chest CT changes on the 14th day after the treatment, the risk of worsening or no change was decreased by 77% in the treatment group versus the control group.

Chest CT Changes	FPV (n=35)	LPV/RTV (n=45)	RR	NNT
Day 14 after treatment Improve Worsen Constant	 32 1 2	 28 9 8	 0.227 (0.0722 to 0.7131)	 3.424

Safety outcome: Antiviral associated outcomes between two groups

"The total number of adverse reactions in the FPV arm of the study was four (11.43%), which was significantly fewer than the 25 adverse reactions (55.56%) in the control arm (P < 0.001). Two patients had diarrhea, one had a liver injury, and one had a poor diet in the FPV arm. Meanwhile, there were five patients with diarrhea, five with vomiting, six with nausea, four with rash, three with liver injury, and two with chest tightness and palpitations in the control arm."
In terms of total adverse events, the risk in the treatment group was decreased by 79% in the treatment group VS the control group.

Chest CT Changes	FPV (n=35)	LPV/RTV (n=45)	RR
Total AE With Without	 4 31	 25 20	 0.21 (0.0789 to 0.5365)
Diarrhea With Without	 2 33	 5 40	 0.51 (0.1060 to 2.4949)
Vomiting With Without	 0 35	 5 40	 0.12 (0.0066 to 2.0326)
Nausea With Without	 0 35	 6 39	 0.10 (0.0057 to 1.6878)
Rash With Without	 0 35	 4 41	 0.14 (0.0079 to 2.5522)

Liver and kidney injury With Without	 1 34	 3 42	0.43 (0.0466 to 3.9448)
Others With Without	 1 34	 2 43	0.64 (0.0607 to 6.8051)

4. APPLICABILITY

In terms of age and sex of the patients in the study, participants are comparable to the Filipino population. Nevertheless, it is important to note that the study did not take note of comorbidities of the study participants which is a possible factor to consider in determining treatment success outcome and adverse events. The study also narrated that severe cases of patients with COVID-19 and those with diagnoses of COVID-19 for more than seven (7) days were excluded in the study. Therefore, results may only be applicable to mild to moderate cases of COVID-19. Based on these points, there is no conclusive evidence to say that the study can also be applicable to the Filipino population.

5. CONCLUSION

There was high risk of selection bias, performance bias and detection bias; selective reporting; and, low risk of attrition bias. Overall, the study has low validity.

Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial [Preprint status]

Author: Chen et. al. (2020)

Critical Appraisal

Reference: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v1.full.pdf

1. DIRECTNESS

Research Question	
P	Adult patients diagnosed with COVID-19 pneumonia who were admitted to 3 hospitals in Wuhan from Feb 20, 2020 to Mar 12, 2020. (N = 236) *"Patients were eligible if they met all the following criteria: (1) aged 18 years or older; (2) voluntarily signed informed consent; (3) the initial symptoms were within 12 days; (4) diagnosed as COVID-19 pneumonia."* *Page 8 Paragraph 2*
I	Favipiravir + standard care (N = 116); 98 were classified as ordinary patients and 18 were critical patients; among the intervention group, 42 have hypertension and/ or diabetes *"The experimental group (favipiravir) was treated with routine treatment + favipiravir tablets (1600 mg/time on the first day, twice a day; 600 mg/time from the second day to the end of the experiment, twice a day).... The course of treatment in both groups was 7-10 days. If necessary, the treatment time could be extended to 10 days according to the judgment of researchers."* *"... (1) Ordinary COVID-19 patients: has a fever, respiratory symptom, can be observed by imageology methods. (2) Critical COVID-19 patients: meeting any of the following case: a. dyspnea, RR > 30 times/min; b. the SpO2 < 93% in the resting state; c. PaO2/FiO2 < 300mmHg (1 mmHg = 0.133 kPa). PaO2/FiO2 should be corrected according to the formula: PaO2/FiO2 × [atmospheric pressure (mmHg)/760]. The pulmonary imaging showed that the lesions progressed more than 50% within 24-48 hours, and the patients were classified as critical patients."* *Page 9 Paragraph 1*
C	Arbidol + standard care (N = 120); 111 were classified as ordinary patients and 9 were critical patients; among the control group, 35 have hypertension and/ or diabetes *"The control group (arbidol) was treated with routine therapy + arbidol (200 mg each time, 3 times a day, from the first day to the end of the trial) The course of treatment in both groups was 7-10 days. If necessary, the treatment time could be extended to 10 days according to the judgment of researchers."* *Page 9 Paragraph 1*
O	Primary outcome: Clinical recovery rate at 7 days or end of treatment *"The primary outcome was the clinical recovery rate at 7 days or the end of treatment, which was stratified as ordinary patients with COVID-19, critical patients with COVID-19, COVID-19 patients with hypertension and/or diabetes. The recovery of fever, respiratory rate, oxygen saturation and cough relief after treatment were defined as clinical recovery, and the recovery state lasted no less*

	than 72 hours. It needs to meet several conditions: axillary temperature ≤ 36.6 °C; respiratory frequency ≤ 24 times/min; Oxygen saturation ≥ 98% without oxygen inhalation; mild or no cough. The armpit temperature, respiratory rate, oxygen saturation without oxygen, oxygen therapy and noninvasive positive pressure ventilation (NPPV) were recorded in daily follow-up. Repeated measurements were made at least twice in each follow-up. The measurements were taken after 15 minutes rest at room temperature (23±2 °C)." Secondary outcomes: · Time from randomization to fever reduction (patients with fever at the time of enrollment) · Time from randomization to cough relief (patients with moderate or severe cough at the time of enrollment) · Rate of auxiliary oxygen therapy or noninvasive mechanical ventilation during the trial · All-cause mortality during the trial · Rate of respiratory failure during the trial (defined as SPO2 ≤ 90% or PaO2/FiO2 < 300 mmHg without oxygen inhalation, and requires oxygen therapy or higher respiratory support). Safety outcomes: Blood biochemistry, urine routine, coagulation function, C-reactive protein, nucleic acid and CT *"Blood biochemistry, urine routine, coagulation function, C-reactive protein, nucleic acid and CT were examined on the third day (D3±1 day) and the seventh day (D7±1 day) after taking the drug, and the adverse events and concomitant medication were observed."* *Page 9-10*

2. APPRAISAL OF VALIDITY

2.1. Were the patients randomly assigned to treatment groups? (Randomization)

Yes

In this study, according to the proportion of 1:1 between the treatment group (favipiravir) and the control group (arbidol), the randomized open label was produced by professional statistical software SAS9.4.

Page 8

2.2. Was allocation concealed? (Allocation Concealment)

Not mentioned

2.3. Were baseline characteristics similar at the start of the trial?

No. While there is no significant difference statistically, the absolute numbers show that there was higher number of patients aged >65 years old in the control group (i.e., 41/120) vs the treatment group (i.e., 29/116). However, in terms of severity, the absolute number of critical patients in the treatment group was double than that of the control group (18/116 and 9/120, respectively).

2.4. Were patients blinded to treatment assignment?

No

The study design was randomized open label.

2.5. Were caregivers blinded to treatment assignments?

No

The study design was randomized open label.

2.6. Were outcome assessors blinded to treatment assignment?

No

The study design was randomized open label.

2.7. Were all patients analyzed in the groups to which they were originally randomized?

Yes

All patient assigned to each group are accounted for and their outcomes noted.

2.8. Was follow-up rate adequate?

Yes

All patients assigned to each group are accounted for and their outcomes noted. There are no drop-outs.

3. APPRAISING THE RESULTS

3.1. How large is the effect treatment?

The outcomes were originally analyzed using log rank test for the recovery rate and Wilcoxon rank sum test for the secondary outcomes. As data were provided in the paper, we are able to calculate for comparative values for the outcomes.

Primary clinical efficacy outcome: Clinical Recovery at Day 7

From our calculation of RR converted from clinical recovery rate, favipiravir was more beneficial among mild cases compared to arbidol, but results were inconclusive among critical cases.

Table 1. RR for clinical recovery at Day 7 at the end of the treatment

Patient population	RR (95%CI)
Total cases	1.18 (0.95 to 1.48)
Ordinary cases	1.27 (1.04 to 1.57)
Critical cases	0.56 (0.04 to 7.96)
Patients with HTN and/or diabetes	1.06 (0.70 to 1.63)

**Mild cases - Ordinary COVID-19 patients: has a fever, respiratory symptom, can be observed by imageology methods; Critical cases - meeting any of the following case: a. dyspnea, RR > 30 times/min; b. the SpO2 < 93% in the resting state; c. PaO2/FiO2 < 300mmHg (1 mmHg = 0.133 kPa).*

Secondary clinical efficacy outcome: need for auxiliary oxygen therapy or non-invasive mechanical ventilation

As regards the need for auxiliary oxygen therapy or non-invasive mechanical ventilation, the results were inconclusive on the benefit of favipiravir across all cases and in subgroupings.

Table 2. RR for the need for auxiliary oxygen therapy or non-invasive mechanical ventilation

Patient population	RR (95%CI)
Total cases	0.80 (0.48 to 1.34)
Ordinary cases	0.48 (0.22 to 1.04)
Critical cases	0.76 (0.56 to 1.03)
Patients with HTN and or diabetes	0.75 (0.34 to1.64)

Mortality

All-cause mortality = 0

Clinical safety outcome: Antiviral-associated adverse effects (AEs) between two groups

Our calculation shows that the risk for AEs were inconclusive except for raised serum uric acid showing five times higher risk in the treatment group versus the control group. We noticed, however, that the numbers reflected in the paper for the reporting of the AEs were inconsistent.

Table 3. RR for the antiviral-associated adverse effects (AEs) between two groups

Patient Population	RR (95% CI)
Total Cases	1.37 (0.9 to 2.08)
LFT abnormal	0.78 (0.34 to 1.77)
Raised serum uric acid	5.52 (1.65 to 18.44)
Psychiatric symptom reactions	2.07 (0.19 to 22.51)
Digestive tract reactions	0.97 (0.52 to 1.83)

4. APPLICABILITY

In terms of age and sex of the patients in the study, participants are comparable to the Filipino population. Comorbidities of the patients include hypertension and diabetes which are also identified as among the top causes of morbidity in the Philippines. It was found that favipiravir may present benefits in the rate of clinical recovery at day 7 among mild cases compared to those given arbidol but results were inconclusive for severe cases. Therefore, results may only be applicable to mild to moderate cases of COVID-19. Based on these points, there is no conclusive evidence to say that the study can also be applicable to severe cases of patients diagnosed with COVID-19 in the Philippines.

5. CONCLUSION

There was high risk of selection bias, performance bias and detection bias; and, low risk of attrition bias. Overall, the study has low validity.