Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among patients with COVID-19, should favipiravir be used for treatment?

Update by: Carla Marie L. Asis, MD, Carol Stephanie C. Tan-Lim, MD, MSc, Natasha Ann R. Esteban-Ipac, MD

Initial review by: Maria Vanessa V. Sulit, BSN, RN, MSc, Anna Garcia RPh, GDip(Epi), Howell Henrian G Bayona, MSc, CSP-PASP

RECOMMENDATION

There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19. *(Low certainty of evidence)*

Consensus Issues
Results from the study are mostly inconclusive and there are still no recommendations on the use of favipiravir outside clinical trials. There are ongoing clinical trials, including one local study currently recruiting participants. Results from these ongoing studies will help further evaluate the use of favipiravir in the treatment of COVID-19.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19, unless in the context of a clinical trial. *(Very low certainty of evidence)*

Previous Consensus Issues
Given that there are on-going clinical trials on favipiravir, the recommendation explicitly stated that there was no recommendation on the use of favipiravir unless it will be used for clinical trials. In addition, there may be some implications with regard to possible reimbursements and will encourage patients to join the clinical trial.

What's new in this version?

This version includes data from one (1) multi-center randomized trial, which included SARS-CoV-2 RNA recurrent positive patients.

Key Findings

Seven (7) randomized controlled trials (RCTs) were found on the use of favipiravir among patients with COVID-19. Pooled results showed a modest benefit in clinical improvement on day 7 favoring favipiravir compared to standard of care; however, clinical improvement on day 28 showed no significant benefit. There was also significant benefit in time to clinical improvement and time to negative conversion. Incidence of viral negative conversion was not significantly different between favipiravir and standard of care. There was no significant difference on the incidence of adverse

events and serious adverse events. Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The overall certainty of evidence was rated low due to serious risk of bias, inconsistency, and very serious imprecision in several critical outcomes.

Introduction

Favipiravir is an oral RNA-dependent RNA polymerase inhibitor used as treatment for influenza and other RNA viruses.[2] It has also been shown to induce lethal mutations of viral RNA, resulting in viral load reduction. It is a potentially effective treatment for SARS-CoV-2.[1] Because of these, as well as recent clinical experience on its use for patients with COVID-19, several studies have been done to assess its clinical efficacy against coronavirus infections.

Review Methods

An updated systematic search was done from the date of last search March 31, 2021 until September 11, 2021 through MEDLINE, Cochrane Central, and Google Scholar using a combined MeSH and free text search coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and favipiravir. The term randomized controlled trial was added as method filter. The COVID-NMA Initiative was also reviewed and was the primary source for most of the RCTs included in this evidence summary as well as the pooled analysis. We searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only RCTs comparing favipiravir alone or with standard of care versus placebo or standard of care were included. We excluded studies that specifically compared favipiravir with other active treatments or as part of a combination treatment.

Results

We found seven (7) RCTs that included 763 adults with RT-PCR confirmed COVID-19 infection ranging from mild to severe.[1-7] Six (6) studies included hospitalized and outpatient adults with newly confirmed COVID-19 infection, while 1 RCT included symptomatic hospitalized and outpatient adults who tested ~~re-~~positive for COVID-19 after hospital discharge with two consecutive negative SARS-CoV-2 RNA tests from the initial infection. Favipiravir was used in different dosing strategies either alone or in combination with standard or supportive care, then compared to standard care. The characteristics of the included studies are summarized in Appendix 3.

Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The overall certainty of evidence was rated low due to serious risk of bias, inconsistency, and very serious imprecision in the critical outcomes. All 7 studies had issues with performance bias. The risk of bias summary is in Appendix 4. The GRADE Evidence Summary is in Appendix 5.

Pooled results of three (3) studies [1,4,5] monitoring clinical improvement on day 7 (Figure 1) showed a modest effect favoring favipiravir compared to standard care with a relative risk (RR) of 1.58 (95% CI 1.15-2.16; I^2 = 0%). However, clinical improvement on day 28 based on five (5) studies [1,2,4-6] (Figure 2) showed no clinical significance at an RR of 1.02 (95% CI 0.95-1.09; I^2 = 0%).[9] Time to clinical improvement favored favipiravir in the pooled results of 3 studies [4-6] with an HR of 1.74 (95% CI 1.33-2.27; I^2 = 43.6%) [8] (Figure 3). There was no significant difference in WHO progression score level 7 or above at day 28 between favipiravir and standard of care (RR 0.33, 95% CI 0.01-8.05; I^2 = 0%) (Figure 4).

All-cause mortality by day 28 was monitored by five (5) studies, with only 2 studies reporting a death in the standard care group. Pooled effect also showed no significant difference between favipiravir and standard of care (RR 0.33 95% CI 0.04-3.16; $I^2 = 0\%$) (Figure 5).[1,3,4,6,7]

Incidence of viral negative conversion (Figures 6 and 7) was not significantly different between favipiravir and standard of care on day 3 (RR 1.22, 95% CI 0.99-1.50; $I^2 = 0\%$) based on pooled results from 3 studies [1,5,6] and on day 30 (RR 1.53, 95% CI 0.97–2.41; $I^2 = 0\%$; 1 RCT). However, for viral negative conversion on day 7 (based on 6 RCTs), although there is no significant difference between favipiravir and the standard of care, there is borderline heterogeneity (RR 1.10, 95% CI 0.96-1.27; $I^2 = 44\%$; p = 0.07). The time to negative conversion favored favipiravir compared to standard care with a pooled HR of 1.40 (95% CI 1.11-1.76; $I^2 = 0\%$) based on 3 studies (Figure 8).[5-7]

Pooled results on the incidence of adverse events showed no significant difference between favipiravir and standard care, however there was moderate~~borderline~~ heterogeneity (RR 1.37, 95% CI 0.90-2.06; $I^2 = 64\%$; p = 0.03) (Figure 7). Adverse events from the studies ranged from hyperuricemia, hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, to cardiac effects like bradycardia and chest pain.[1-7]

Serious adverse events such as acute respiratory distress syndrome, death from heart failure, bone fracture, and increasing oxygen desaturation were also reported in the studies. Pooled results also showed no significant difference between favipiravir and standard of care (RR of 1.45, 95% CI 0.59-3.55; $I^2 = 0\%$) (Figure 10).[8]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
NIH COVID-19 Treatment Guidelines (as of September 3, 2021)	No recommendations on the use of favipiravir for the treatment of COVID-19.[8-10]
Surviving Sepsis Campaign Guidelines (as of January 29, 2021)	
Infectious Diseases Society of America (as of September 3, 2021)	
Australian Guidelines for Clinical Care of People with COVID-19 (as of August 27, 2021)	Recommends against the use of favipiravir for the treatment of COVID-19 unless in the context of a randomized trial with appropriate ethical approval.[11]

Research Gaps

There are 24 ongoing trials on favipiravir compared to placebo or standard care listed in various clinical trial registries. An open label randomized controlled multi center trial in the Philippine setting has recently been registered at the NIH – U.S. National Library of Medicine's *clinicaltrials.gov* and is currently recruiting adult patients with non-severe disease. Updates will be added to this review as soon as results from these trials are available.

References

[1] Lou Y, Liu L, Yao H, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. *Eur J Pharm Sci.* 2021;157:105631. doi:10.1016/j.ejps.2020.105631

[2] Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. *Clin Infect Dis*. 2021;73(3):531-534. doi:10.1093/cid/ciaa1176

[3] Dabbous HM, El-Sayed MH, El Assal G, et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial. *Sci Rep*. 2021;11(1):7282. Published 2021 Mar 31. doi:10.1038/s41598-021-85227-0

[4] Balykova L.A., Granovskaya M.V., Zaslavskaya K.Ya., Simakina E.N., Agaf'ina A.S., Ivanova A.Yu., Kolontarev K.B., Pushkar D.Yu. New possibilities for targeted antiviral therapy for COVID-19. Results of a multicenter clinical study of the efficacy and safety of using the drug Areplivir. Infektsionnye bolezni: novosti, mneniya, obuchenie [Infectious Diseases: News, Opinions, Training]. 2020; 9 (3): 16–29. DOI: https://doi.org/10.33029/2305-3496-2020-9-3-16-29 (in Russian)

[5] Ruzhentsova TA, Chukhliaev PV, Khavkina DA, Garbuzov AA, Oseshnyuk RA, Soluyanova TN, et. al. Phase 3 Trial of Coronavir (Favipiravir) in patients with mild to moderate COVID-19, https://ssrn.com/abstract=3696907

[6] Udwadia ZR, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et, al. International Journal of Infections Diseases. 2021; 103:62-71 https://doi.org/10.1016/j.ijid.2020.11.142

[7] Zhao H, Zhang C, Zhu Q, et al. Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial. *Int Immunopharmacol*. 2021;97:107702. doi:10.1016/j.intimp.2021.107702

[8] The COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/

[9] NIH - Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, https://www.covid19treatmentguidelines.nih.gov/

[10] Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19), https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

[11] Infectious Disease Society of America Guidelines on the Treatment and Management of Patients with COVID-19, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

[12] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v42.1 2021 August 27, https://app.magicapp.org/#/guideline/L4Q5An

[13] NIH – U.S. National Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cond=Covid19+OR+coronavirus&term=favipiravir&cntry=&state=&city=&dist=

[14] Chinese Clinical Trials Registry, ChiCTR, http://www.chictr.org.cn/searchprojen.aspx?title=&officialname=&subjectid=&secondaryid=&applier=&studyleader=&ethicalcommitteesanction=&sponsor=&studyailment=&studyailmentcode=&studytype=0&studystage=0&studydesign=0&minstudyexecutetime=&maxstudyexecutetime=&recruitmentstatus=0&gender=0&agreetosign=&secsponsor=&regno=&regstatus=0&country=&province=&city=&institution=&institutionlevel=&measure=favipiravir&intercode=&sourceofspends=&createyear=0&isuploadrf=&whetherpublic=&btngo=btn&verifycode=&page=1

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 6)

FACTORS	JUDGEMENT (N = 6)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large	Moderate (2)	Small (3)	Uncertain (1)			• Time to clinical improvement (HR 1.74, 95% CI 1.33-2.27), and time to negative conversion (HR 1.4, 95% CI 1.11-1.76) favored favipiravir
Harm	Large	Small (4)	Uncertain (2)				• There was no significant difference in the incidence of AE (RR 1.37, 95% CI 0.90-2.06) and SAE (RR 1.45, 95% CI 0.59-3.55)
Certainty of Evidence	High	Moderate (1)	Low (2)	Very low (3)			• Low due to serious risk of bias, inconsistency, and very serious imprecision in several critical outcomes.
Balance of effects	Favors drug (2)	Does not favor drug	Uncertain (4)				• The benefits and harms were both small with no significant difference in most of the main outcomes of interest
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost (5)	Negligible cost	Moderate savings (1)	Large savings	• Favipiravir (Avigan®) has a cost of USD 3 per 200mg tablet (Php 150.456) • Full treatment course requiring a total of 45 tablets per patient will amount to a total treatment cost of Php 9,000 or USD 135 per patient.
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low	Moderate (3)	High (1)		
Cost effectiveness	No included studies (3)	Favors the comparison (2)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (3)	Reduced (1)	Probably no impact (1)	Increased (1)			
Acceptability	Uncertain (3)	No	Yes (3)				
Feasibility	Uncertain (1)	No	Yes (5)				

Appendix 2. Search Yield and Results

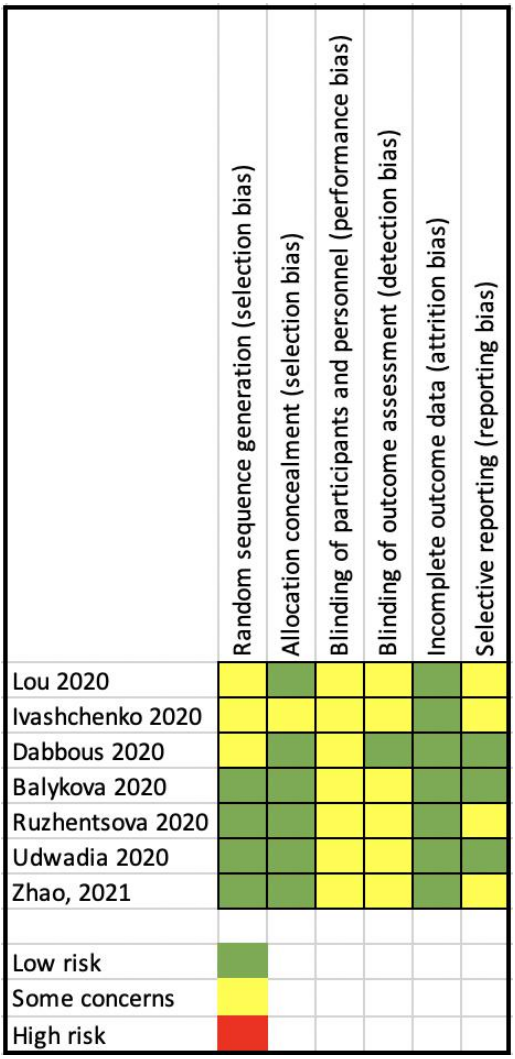
DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND favipiravir Filters: March 31, 2021 to September 11, 2021 and Randomized Controlled Trial	September 11, 2021 2:00PM	7	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND favipiravir AND “Randomized Controlled Trial” Filters: March 31, 2021 to September 11, 2021	September 11, 2021 2:15PM	17	1
COVID-NMA Initiative	Favipiravir	September 11, 2021 3:00PM	14	7
Google Scholar	Favipiravir AND COVID AND randomized controlled trial	September 11, 2021 3:10PM	55	7
ClinicalTrials.gov	Favipiravir Filters: Interventional (Clinical Trial), not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, unknown status	September 11, 2021 3:15PM	33	19
Chinese Clinical Trial Registry	Favipiravir	September 11, 2021 3:18PM	8	1
EU Clinical Trials Register	COVID-19 AND Favipiravir	September 11, 2021 3:20PM	11	9
Republic of Korea - Clinical Research Information Service	Favipiravir	September 11, 2021 3:25PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Favipiravir	September 11, 2021 3:28PM	0	0
CenterWatch	Favipiravir	September 11, 2021 3:29PM	8	4
chinaxiv.org	Favipiravir	September 11, 2021 3:31PM	0	0
Medrxiv.org	Favipiravir Filters: March 31, 2021 to September 11, 2021	September 11, 2021 3:41PM	33	0
Biorxiv.org	Favipiravir Filters: March 31, 2021 to September 11, 2021	September 11, 2021 4:11PM	42	0

Appendix 3: Characteristics of Included Studies

Study & Setting	Treatment Intervention	Comparator	Design & Risk of Bias	Participants & Sample Size	Outcomes
Lou 2020[1] (China)	Favipiravir (1600 or 2200mg initial, then 600mg tid) up to 14 days + existing antiviral treatment	Baloxavir marboxil group: baloxavir marboxil (80 mg od) on day 1 and day 4; for patients who are still positive in virological test, they can be given again on day 7 + existing antiviral treatment Existing antiviral treatment or standard care: Lopinavir/ritonavir (400mg/100 mg bid or darunavir/cobicistat 800 mg/150 mg, qd and arbidol 200 mg tid)	RCT Some concerns in the risk of bias	30 hospitalized adults (ages 18-85) with COVID-19 infection of unclear severity	Primary Viral negative on day 14; Time from randomization to clinical improvement by 2 points on NEWS2 or live discharge (whichever came first) Secondary Viral negative on day 7; Incidence of mechanical ventilation on day 14; ICU Admission on Day 14; All-cause mortality on day 14.
Ivashchenko 2020[2] (Russia)	Favipiravir 1800/800mg (1800mg day 1; 800mg days 2-14) Favipiravir 1600/600mg (1600mg day 1; 600mg days 2-14)	Standard care according to Russian guidelines that included hydroxychloroquine or chloroquine; or lopinavir/ritonavir	RCT Some concerns in the risk of bias	60 hospitalized adults (ages 18 and above) with moderate PCR-confirmed COVID-19 on screening	Primary Elimination of SARS-CoV-2 at day 10 (by 2 negative PCR tests) Secondary Rate of viral clearance by day 5; Time to normalization of clinical symptoms; changes on CT scan by day 15; incidence and severity of adverse events
Dabbous 2020[3] (Egypt)	Favipiravir (600mg up to 10 days)	Standard care defined as Oseltamivir (75 mg 12 hourly for 10 days) and hydroxychloroquine (400 mg 12 hourly on day-one followed by 200 mg 12 hourly daily on day 2 to 10 days) conforming to the national standard of care therapy.	RCT Some concerns in the risk of bias	100 hospitalized adults (ages 18-80) with PCR-confirmed COVID-19 and mild to moderate symptoms according to the national protocol classification	Primary Viral clearance on days 3, 7 and 14 (2 successive negative PCRs 48hrs apart); Normalization of body temperature for 48 hrs; Improvement of radiological abnormalities at day 14 and discharge rate. Secondary Normalization of C-reactive protein and serum ferritin levels
Balykova 2020[4] (Russia)	Favipiravir (1200mg day 1 then 600mg for 14 days)	Standard care in accordance to the Temporary Guidelines of the Ministry of Health of Russia that included hydroxychloroquine + azithromycin; hydroxychloroquine, lopinavir + ritonavir	RCT Some concerns in the risk of bias	200 hospitalized adults (ages 18-80) with PCR-confirmed COVID-19 of moderate severity	Clinical improvement according to the WHO Categorical Scale of Clinical Improvement; Clinical and laboratory data; Improvement of CT scan of the chest organs and the clearance of the SARS-CoV-2 virus; The frequency and nature of the occurrence of adverse events; The need for invasive and non-invasive oxygen support; Mortality
Ruzhentsova 2020[5] (Russia) *Pre-print*	Favipiravir (1800mg bid on day 1, followed by a maintenance dose	Standard care that included either umifenovir (200 mg 4 qid) + intranasal interferon alpha-2b (10000 IU/ml –	RCT Some concerns in	168 hospitalized and outpatient adults (ages	Primary Time to clinical improvement (based on a reduction of patient clinical status on at least 1 score according to WHO 8-Category

	800mg bid on days 2-10)	3 drops in each nasal channel 5 times a day), or hydroxychloroquine (400mg bid on day 1 followed by 200mg bid or 200mg bid on day 1 followed by 100mg bid) during the period up to 10 days, depending on the severity of the condition of the patient	the risk of bias	18-60) with mild to moderate PCR-confirmed COVID-19 w/out respiratory failure	Ordinal Scale for Clinical Improvement compared to screening; Time to viral clearance at day 28 (in 2 negative PCR results) Secondary Rate of clinical improvement at day 7; Viral clearance at day 5; Rate of clinical improvement at day 14; Rate of viral clearance at separate days; Time to body temperature normalization; Rate of resolution of resolution of lung changes on CT at day 14; Time to resolution of main disease symptoms; The rate of artificial lung ventilation; rate of transfer to ICU; Death rate during the 28 days
Udwadia 2020[6] (India)	Favipiravir (1800mg bid on day 1, 800mg bid) + standard supportive care for up to 14 days	Standard care that included antipyretics, cough suppressants, antibiotics, and vitamins (drugs with potential antiviral activity against SARS-CoV-2 and HCQ were prohibited)	RCT Some concerns on the risk of bias	150 hospitalized adults (ages 18-75) with PCR-confirmed COVID-19 and mild to moderate symptoms	Primary Viral clearance on negative RT-PCR result for 2 consecutive times (28 days maximum) and at hospital discharge Secondary Time to clinical cure based on clinician assessment; Time to first use of high flow supplemental oxygen/ ventilation/ECMO; Time to hospital discharge (RT-PCR negativity on 2 consecutive tests); Adverse events
Zhao, 2021[7] (China)	Favipiravir (1600mg bid on day 1 then 600mg bid from day 2 to 7) + standard treatment up to 14 days	Standard care	RCT Some concerns in the risk of bias	55 hospitalized and outpatient adults (ages 28-79) who tested re-positive for SARS-CoV-2 RNA by nasopharyngeal swab RT-PCR after discharge with mild to severe symptoms	Primary Time to achieve a consecutive twice (at intervals of >24 h) negative RT-PCR result for SARS-CoV-2 RNA in nasopharyngeal swab and sputum sample Secondary Adverse events

Appendix 4. Study Appraisal



Appendix 5. GRADE Evidence Profile

Author(s): Carla Marie L. Asis, MD
Question: Favipiravir compared to Standard care for COVID-19
Setting: Worldwide
Bibliography: 1. Lou Y, Liu L, Yao H, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur J Pharm Sci. 2021;157:105631. doi:10.1016/j.ejps.2020.105631 2. Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clin Infect Dis. 2021;73(3):531-534. doi:10.1093/cid/ciaa1176 3. Dabbous HM, El-Sayed MH, El Assal G, et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial. Sci Rep. 2021;11(1):7282. Published 2021 Mar 31. doi:10.1038/s41598-021-85227-04. Balykova L.A., Granovskaya M.V., Zaslavskaya K.Ya., Simakina E.N., Agaf'ina A.S., Ivanova A.Yu., Kolontarev K.B., Pushkar D.Yu. New possibilities for targeted antiviral therapy for COVID-19. Results of a multicenter clinical study of the efficacy and safety of using the drug Areplivir. Infektsionnye bolezni: novosti, mneniya, obuchenie [Infectious Diseases: News, Opinions, Training]. 2020; 9 (3): 16–29. DOI: https://doi.org/10.33029/2305-3496-2020-9-3-16-29 (in Russian)5. Ruzhentsova TA, Chukhliaev PV, Khavkina DA, Garbuzov AA, Oseshnyuk RA, Soluyanova TN, et. al. Phase 3 Trial of Coronavir (Favipiravir) in patients with mild to moderate COVID-19, https://ssrn.com/abstract=36969076. Udwadia ZR, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et, al. International Journal of Infections Diseases. 2021; 103:62-71 https://doi.org/10.1016/j.ijid.2020.11.1427. Zhao H, Zhang C, Zhu Q, et al. Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial. Int Immunopharmacol. 2021;97:107702. doi:10.1016/j.intimp.2021.107702

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Standard care	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement (follow-up: 7 days)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	88/216 (40.7%)	36/163 (22.1%)	**RR 1.58** (1.15 to 2.16)	**128 more per 1,000** (from 33 more to 256 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical improvement (follow-up: 28 days)												
5	randomised trials	Serious[b]	not serious	not serious	not serious	none	209/327 (63.9%)	139/252 (55.2%)	**RR 1.02** (0.95 to 1.09)	**11 more per 1,000** (from 28 fewer to 50 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Time to clinical improvement (follow-up: 28 days)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	287	231	-	HR **1.74 higher** (1.33 higher to 2.27 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
All-cause mortality (follow-up: mean 26.4 days)												
5	randomised trials	Serious[c]	not serious	not serious	Serious[d]	none	0/274 (0.0%)	2/251 (0.8%)	**RR 0.33** (0.04 to 3.16)	**5 fewer per 1,000** (from 8 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (follow-up: mean 28.8 days)												
5	randomised trials	Serious[c]	Serious[e]	not serious	Serious[d]	none	161/363 (44.4%)	79/270 (29.3%)	**RR 1.37** (0.90 to 2.06)	**108 more per 1,000** (from 29 fewer to 310 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow-up: mean 26 days)												
5	randomised trials	Serious[c]	not serious	not serious	Serious[d]	none	9/333 (2.7%)	5/260 (1.9%)	**RR 1.45** (0.59 to 3.55)	**9 more per 1,000** (from 8 fewer to 49 more)	⨁⨁◯◯ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Issues in performance and detection bias in included studies
b. Issues on selection, performance, detection, and reporting bias
c. Issues on selection, performance, and detection bias
d. Wide confidence interval
e Significant heterogeneity (I2=64%)

Appendix 6. Forest Plots

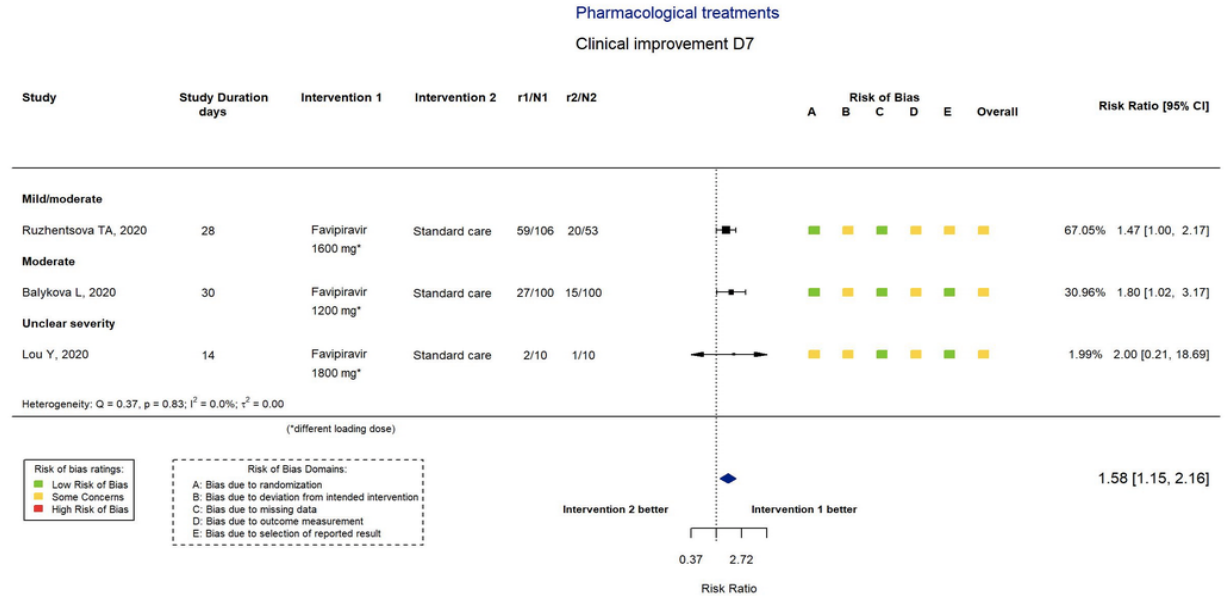


Figure 1. Clinical Improvement Day 7
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

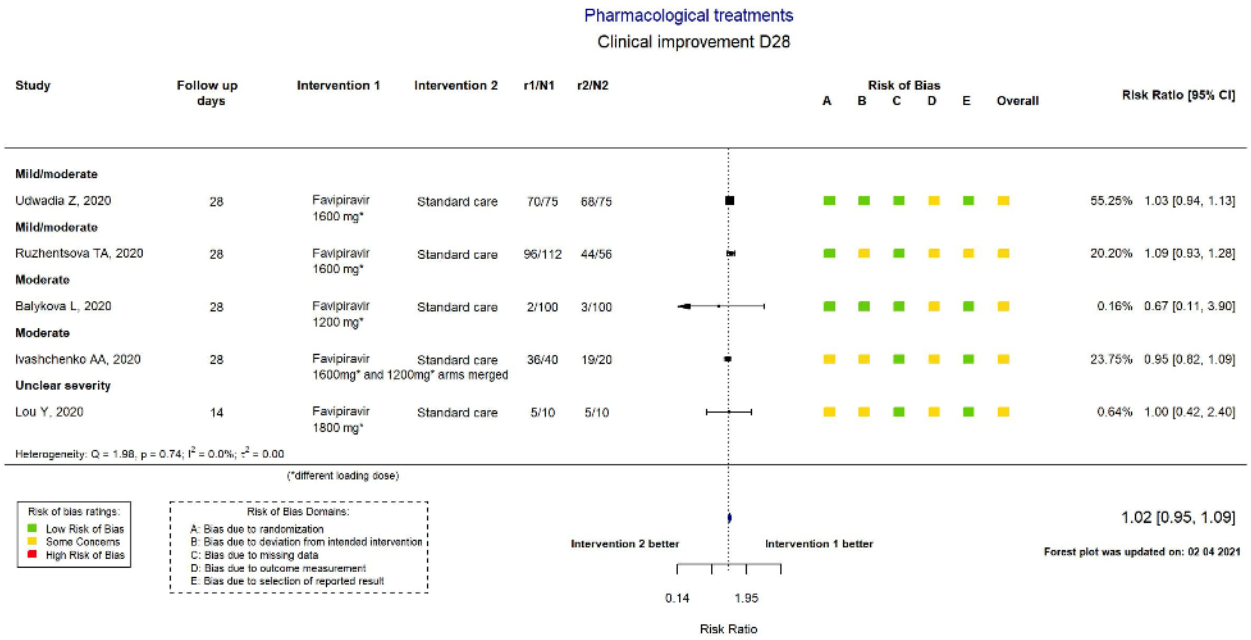


Figure 2. Clinical Improvement Day 28
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

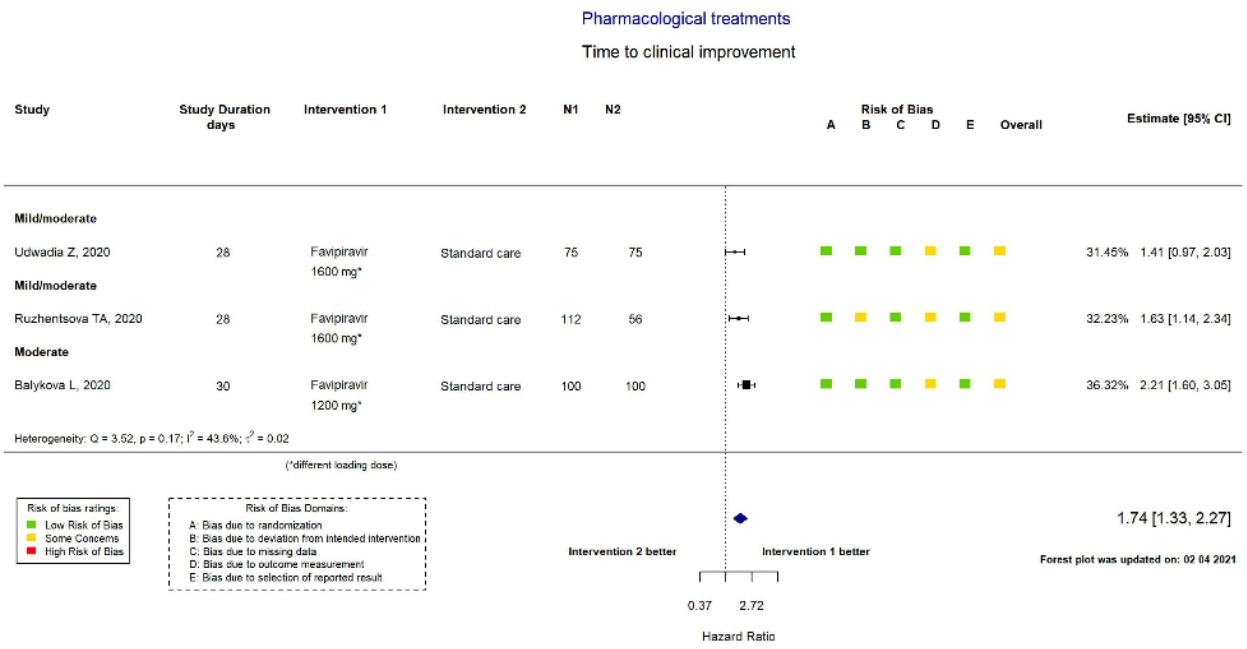


Figure 3. Time to Clinical Improvement
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

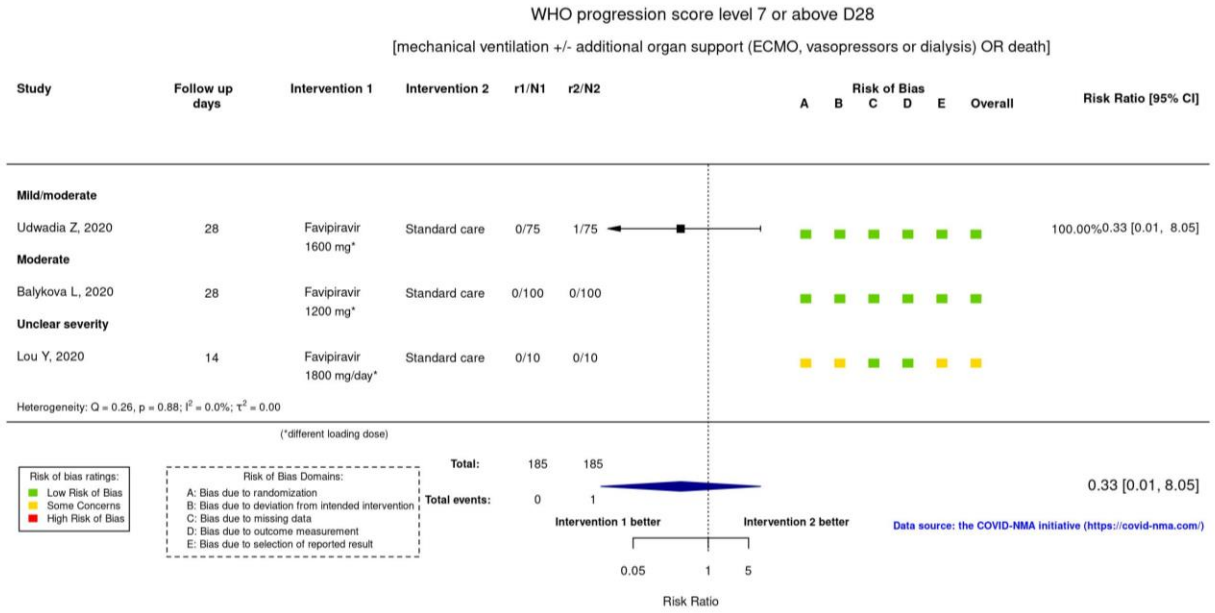


Figure 4. WHO progression score
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

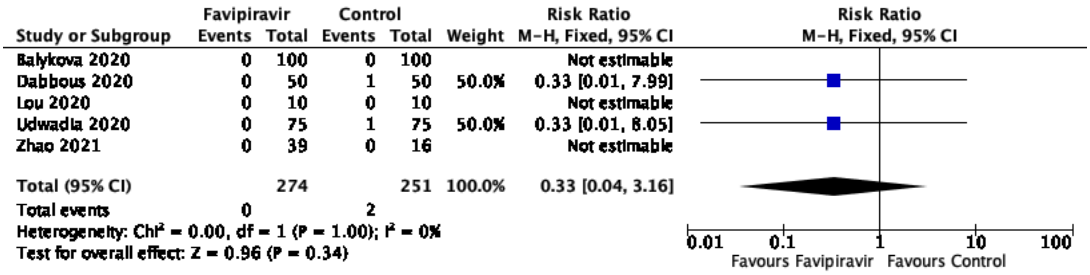


Figure 5. All-cause mortality

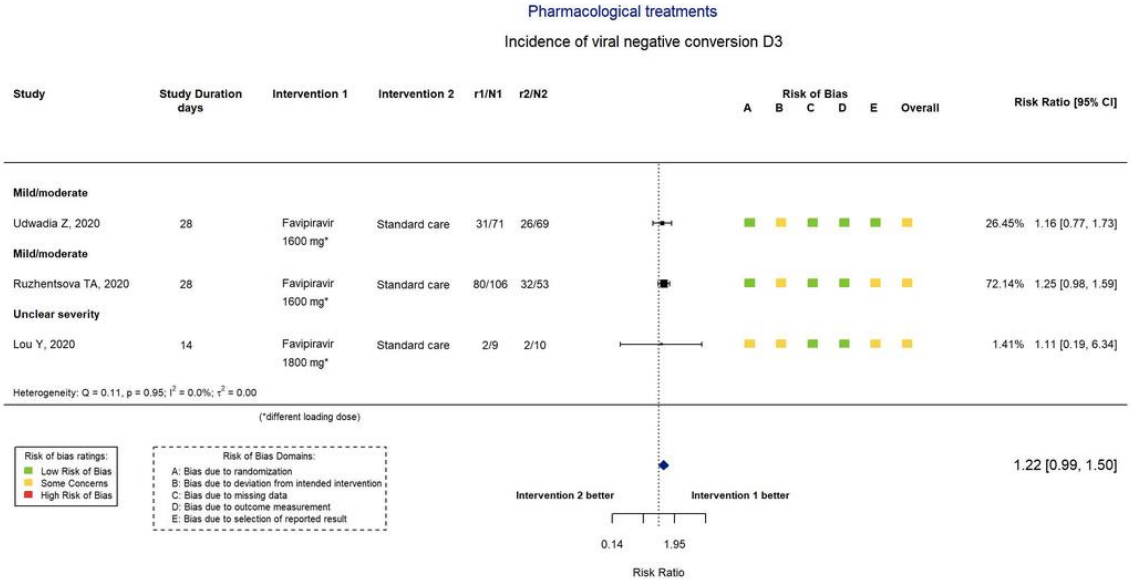


Figure 6. Incidence of Viral Negative Conversion Day 3
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

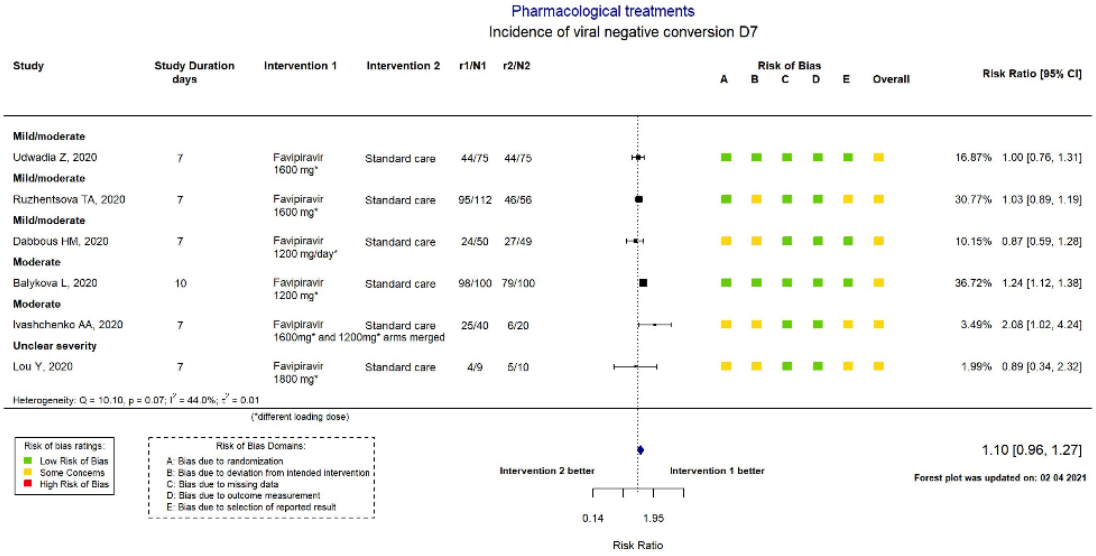


Figure 7. Incidence of Viral Negative Conversion Day 7
(from the COVID-NMA initiative: A living mapping and living systematic review of Covid-19 trials, https://covid-nma.com/)

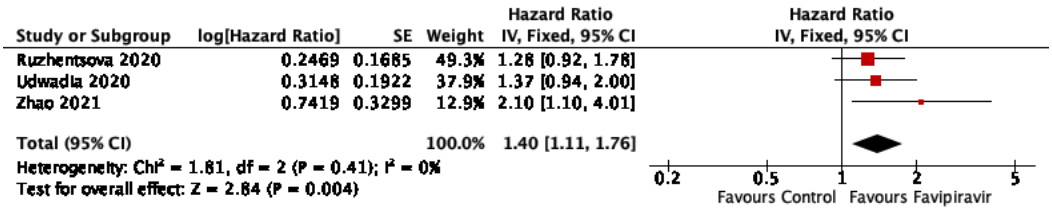


Figure 8. Time to Negative Conversion

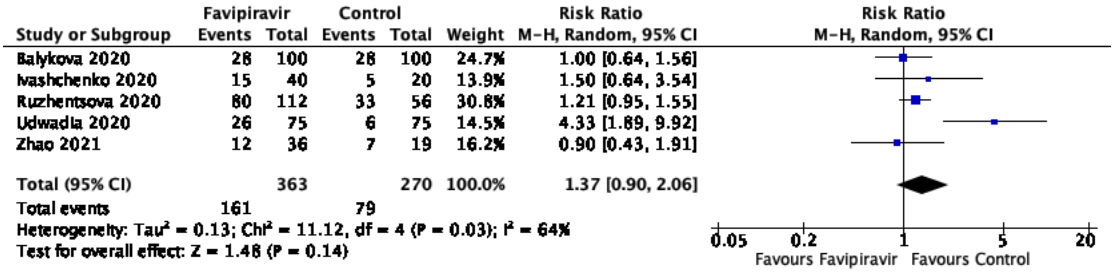


Figure 9. Adverse Events

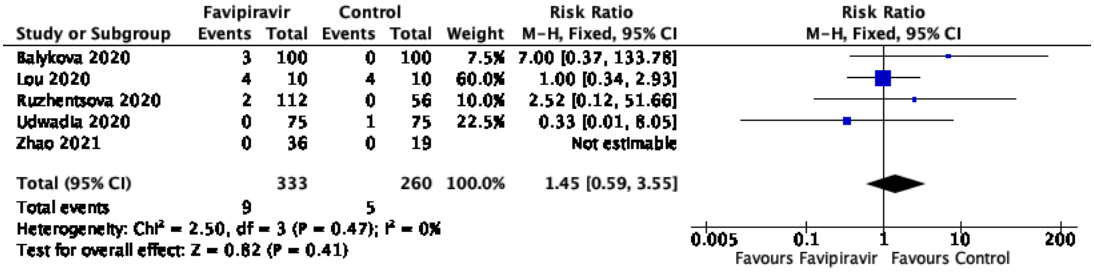


Figure 10. Serious Adverse Events

Appendix 7. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Efficacy of Favipiravir in Treatment of Mild & Moderate COVID-19 Infection in Nepal *Phase 3*	18 to 80 years confirmed COVID-19 by RT-PCR, mild to moderate	**MILD DISEASE** Experimental: Favipiravir (1800mg BID on day 1, 800mg BID from day 2 up to 5 days) Control: Placebo **MODERATE DISEASE** Experimental: Favipiravir (1800mg BID on day 1, 800mg BID from day 2 up to 10 days) Control: Remdesivir (200mg IV on day 1 then 100mg IV daily up to 10 days)	Primary outcome: Time to clinical improvement	Randomized, parallel assignment, open label
2. Clinical Trial of Favipiravir Treatment of Patients With COVID-19 *Phase 3*	18 to 74 years SARS-CoV-2 positive patients as measured by RT-PCR by nasopharyngeal sampling, hospitalized, moderate	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID on day 2-14) Control: Supportive care (symptomatic therapy)	Primary outcome: Time to improvement in body temperature; Time to improvement in SpO2; Time to improvement in chest imaging findings; Time to improvement in negative SARS-CoV-2	Randomized, parallel assignment, open label
3. The Prevent Severe COVID-19 (PRESECO) Study *Phase 3*	18 years or older, tested positive for SARS-CoV-2 by RT-PCR assay using a respiratory tract sample, mild to moderate, non-hospitalized	Experimental: Favipiravir Control: Placebo	Primary outcome: Time to sustained clinical recovery	Randomized, parallel assignment, triple-blind, placebo-controlled
4. Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients *Phase 3*	21 to 80 years confirmed COVID-19 by RT-PCR, hospitalized, moderate or severe	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID for next 9 days maximum) + supportive care Control: Placebo + standard of care	Primary: Time to resolution of hypoxia (Stage I)	Randomized, parallel assignment, double-blind, placebo-controlled
5. Clinical Study To Evaluate The Performance And Safety Of Favipiravir in COVID-19 *Phase 3*	18 to 75 years confirmed COVID-19 by RT-PCR, moderate	Experimental: Favipiravir (1800mg BID on day 1, 600mg TID on day 2 up to 14 days) Control: Placebo	Primary: Time from randomization to clinical recovery	Randomized; parallel assignment, double-blind, placebo-controlled
6. A Trial of Favipiravir Therapy in Adults With Mild Coronavirus Disease COVID-19 *Phase 2/3*	At least 18 years confirmed COVID-19 by PCR, mild	Experimental: Favipiravir (1800mg BID on day 1, then 800mg BID up to 7 days) Control: Placebo	Primary: Time from randomization to negativity in RT-PCR nucleic acid test for COVID-19 within 15 days of randomization	Randomized; parallel assignment, double-blind, placebo-controlled
7. An Adaptive Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19 *Phase 2/3*	18 years and older confirmed COVID-19 by RT-PCR, hospitalized with moderate severity	Experimental: Favipiravir, lower dose (pilot stage; 1600mg BID on the 1st day followed by 600mg BID for 13 days) Favipiravir, higher dose (pilot stage; 1800mg BID on the 1st day followed by 800mg BID for 13 days)	Primary: Rate of viral elimination by Day 10 [pilot stage, dose selection]; Time to viral elimination [pivotal stage]; Time to clinical improvement [pivotal stage]	Randomized; sequential assignment, open label

		Dose for pivotal stage will be selected based on pilot study results. Control: Standard of care (pilot stage & pivotal stages; might include hydroxychloroquine, chloroquine, lopinavir/ritonavir or other recommended schemes)		
8. A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase 3 Study Evaluating Favipiravir in Treatment of COVID19 *Phase 3*	18 to 75 years confirmed COVID-19 by RT-PCR, moderate	Experimental: Favipiravir (1800mg BID on day 1, 600mg TID on day 2 up to 14 days) + supportive care Control: Placebo	Primary: Time from randomization to clinical recovery	Randomized; parallel assignment, double-blind, placebo-controlled
9. Safety and Efficacy of Maraviroc and/or Favipiravir With Standard Therapy in Severe COVID-19 Adults *Phase 2*	18 to 70 years confirmed COVID-19 by RT-PCR within 12 days post appearance of symptoms, hospitalized, severe, non-critical	Experimental: Maraviroc + currently used therapy for non-critical COVID patients (CT) Favipiravir + CT Maraviroc + Favipiravir + CT Control: CT (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present)	Primary: Percentage of patients free of mechanical ventilation or death	Randomized; parallel assignment, open label
10. Study on Safety and Efficacy of Favipiravir (Favipira) for COVID-19 Patient in Selected Hospitals of Bangladesh *Phase 2/3*	18 to 65 years, respiratory samples tested positive for the novel coronavirus, non-severe	Experimental: Favipiravir 1600mg BID on day 1, 600mg BID on days 2-10 Control: Standard treatment (oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, antibiotics and antiemetic drugs & the medication any patient is on due to any concomitant diseases)	Primary: Number of participants negative by RT-PCR for the virus at 4-10 days after initiation of therapy; Number of participants with lung condition change assessed with X-ray	Randomized, parallel assignment, double-blind, placebo-controlled
11. Favipiravir in High-risk COVID-19 Patients *Phase 3*	50 years and older, confirmed COVID-19 by RT-PCR, mild to moderate	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID on days 2-5) Control: Standard of care only	Primary: Need for oxygen supplement	Randomized, parallel assignment, open label
12. Philippine Trial to Determine Efficacy and Safety of Favipiravir for COVID-19 *Phase 3*	18-74 years SARS-CoV-2-positive nasopharyngeal swab by RT-PCR test, non-severe presentation	Experimental: Favipiravir (1800mg bid on day 1, then 800mg bid from day 2 up to 14 days) + best supportive care or standard treatment Control: Best supportive care or standard treatment (oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, antibiotics and antiemetic drugs & the medication any patient is on due to any concomitant diseases)	Primary: Time from initiation of treatment to clinical improvement	Randomized, parallel assignment, open label
13. Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive	18 TO 80 years diagnosed with COVID-19, and the nucleic acid test of respiratory specimens such as sputum or nasopharyngeal swabs has been negative for two consecutive times after treatment (sampling time interval of at least 24	Experimental: Favirapir (1600mg BID on day 1; 600mg BID from day 2-7 up to 14 days) Control: Regular treatment group (treatments other than lopinavir and ritonavir, chloroquine phosphate, hydroxychloroquine sulfate, arbidol, and colomycin can be given)	Primary outcome: Viral nucleic acid test negative conversion rate	Randomized, parallel assignment, open label

	hours); The nucleic acid test of specimens such as sputum, throat swabs, blood, feces and other specimens was positive for COVID-19 during screening visits.			
14. An Adaptive Clinical Trial of Antivirals for COVID-19 Infection *Phase 2*	18 years and older confirmed SARS-CoV-2 by nucleic acid testing	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID for the next 13 days) Control: Placebo	Primary outcome: Time to virological cure	Randomized, parallel assignment, quadruple blind, placebo-controlled
15. Early Intervention in COVID-19: Favipiravir Verses Standard Care *Phase 3*	18 years and older suspected or confirmed COVID-19 infection	Experimental: Favipiravir (1800mg BID on day 1, 800mg BID from days 2-10) Control: Standard of care	Primary outcome: Time from randomization to a sustained clinical improvement (maintained for 24 hours) by two points on a seven-category ordinal scale or to discharge, whichever occurs first	Randomized, parallel assignment, open label
16. Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia *Phase 2/3*	18 to 75 years previously diagnosed with novel coronavirus pneumonia: the course of illness is no more than 14 days; if the course of the disease was more than 14 days, patient meets one of the following conditions can also be included in the group: (1) No apparent absorption or progression of chest radiograph was observed within 7 days; (2) respiratory symptoms (chest tightness, or cough, or breathing difficulties); (3) Test for viral nucleic acid positive within 3 days	Experimental: Favipiravir (1600mg BID on day 1, 600mg BID from days 2-10) + chloroquine phosphate (500mg BID on day 1, 500mg OD from days 2-3, 250mg OD from days 4-10) Favipiravir (1600mg BID on day 1, 600mg BID from days 2-10) Control: Placebo	Primary outcome: 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	Randomized, parallel assignment, double-blind
17. Study to Assess the Efficacy and Safety of Favipiravir-HU *Phase 2*	18 to 65 years PCR confirmed SARS-CoV-2 infection, asymptomatic or mild	Experimental: Favipiravir HU + standard of care Control: Placebo HU	Primary outcome: Percentage of virus copy number at Day 6 compared to baseline	Randomized, parallel assignment, double-blind, placebo-controlled
18. Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients With Mild to Moderate COVID-19 *Phase 3*	18 to 60 years, PCR verified SARS-CoV-2 infection, mild or moderate without respiratory failure	Experimental: Favipiravir (1800mg BID on day 1800mg BID from days 2-10) + standard of care Control: Standard of care including etiotropic therapy according to MoH of Russian Federation Recommendations for COVID-19 (umifenovir + intranasal recombinant interferon alpha, or hydroxychloroquine, or chloroquine, or mefloquine in recommended regimen) up to10 days	Primary outcome: Time to clinical improvement defined as reduction on at least 1 score of patient clinical status according to WHO 8-category Ordinal Scale for Clinical Improvement; Time to viral clearance as measured by PCR in oropharyngeal sampling	Randomized, parallel assignment, open label
19. Finding Treatments for COVID-19: A Trial of Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV) *Phase 2*	18 to 50 years previously healthy with early symptomatic COVID-19 SARS-CoV-2 positive by lateral flow antigen test	Experimental: Favipiravir (1800mg BID D0 and 800mg BID for a further 6/7) Ivermectin (600 micrograms/kg/day for 7/7) Remdesivir (200mg D0 and 100mg for a further 4/7) Active comparator: Monoclonal antibodies (1,200mg casirivimab/ 1200mg imdevimab given once on D0)	Primary outcome: Rate of viral clearance for repurposed drugs; Rate of viral clearance of positive control; Rate of viral clearance for small novel molecule drugs	Randomized, parallel assignment, open label

		Control: No treatment (except antipyretics – paracetamol)		
20. Safety and Efficacy of Favipiravir in COVID-19 Patients with Pneumonia −A randomized, double blind, placebo- controlled study *Phase 2*	18 to 85 years, positive for SARS-COV2 on RT-PCR test from respiratory specimen(s), categories 3 to 5 on the WHO ordinal scale	Experimental: Favipiravir Control: Placebo	Primary outcome: Time to clinical improvement measured as improvement for ≥ two categories on a 7-point ordinal scale	Randomized, double-blind, placebo-controlled
21. An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients with Mild Pneumonia *Phase 3*	18 to 74 years SARS-CoV-2-positive airway specimens by RT-PCR, with mild pneumonia	Experimental: Favipiravir Control: Supportive care (symptomatic therapy) up to 14 days	Primary outcome: Time from initiation of the study drug to the time of "improvement" in body temperature, SpO2, and chest imaging and negative SARS-CoV-2	Randomized, open label
22. A Randomised Controlled Trial of Early Intervention in Patients HospItalised with COVID-19: Favipiravir verses HydroxycholorquiNe & Azithromycin & Zinc vErsEs Standard CaRe *Phase 3*	18 years and older, suspected or confirmed COVID-19 infection	Experimental: Favipiravir Hydroxychloroquine Azithromycin Control: UK standard of care for COVID-19 infection	Primary outcome: Time to clinical improvement (post randomisation) by two points on a seven-category ordinal scale or live discharge from the hospital, whichever comes first	Randomized, parallel assignment, open label
23. An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients without Pneumonia *Phase 3*	18 to 74 years SARS-CoV-2-positive airway specimens by RT-PCR, without pneumonia	Experimental: Favipiravir Control: Supportive care (symptomatic therapy) up to 14 days	Primary outcome: Time from initiation of the study drug to the time of "improvement" in body temperature, SpO2, and chest imaging and negative SARS-CoV-2	Randomized, open label
24. Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19) : a multiarm, multi-stage (MAMS) randomized trial to assess the efficacy and safety of several experimental treatments to reduce the risk of hospitalization or death (COVERAGE trial) *Phase 3*	60 years or older with positive test for SARS-CoV-2 on a nasopharyngeal swab	Experimental: Imatinib (400mg qd from day 0-9) Favipiravir (2400mg bid on day 0, 1200mg bid from day 1-9) Telmisartan (20mg qd from day 0-9) Control: Complex of vitamins and trace elements (AZINC Forme et Vitalité®) 1 cap bid for 10 days	Primary outcome: Proportion of participants with an occurrence of hospitalization and/or death between D0 and D14 in each arm	Randomized, parallel assignment, open label