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

RESEARCH QUESTION: **Among COVID-19 patients, should favipiravir be used for treatment?**

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RECOMMENDATION

Recommendation	Certainty of Evidence	Strength of Recommendation
We recommend against the use of favipiravir among patients with COVID-19	Moderate	Strong

Consensus Issues
The consensus panel strongly recommended against the use of favipiravir among patients with COVID-19, based on a moderate certainty evidence that it has no benefit in any of the critical outcomes (i.e. all-cause mortality, clinical improvement, clinical deterioration or need for hospitalization). Furthermore, the panelists also recognize another important outcome, where patients who received favipiravir had significantly higher risk of adverse events, such as hyperuricemia, hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, and cardiac effects like bradycardia and chest pain. As of writing, there are 20 ongoing clinical trials among adults, the results of which may further elucidate on the use of favipiravir in COVID-19 treatment.

KEY FINDINGS

- A total of twenty-two (22) randomized controlled trials (RCTs) were found on the use of favipiravir among patients with COVID-19.
- Favipiravir has no significant benefit on all-cause mortality, clinical improvement, symptom progression, time to recovery, nor hospitalization.
- Pooled results show favipiravir had a significant benefit in viral negative conversion by day 7.
- Favipiravir has significantly more reported adverse events, especially in the inpatient subset, while no significant difference was seen for serious adverse events.
- The overall certainty of evidence was rated moderate due to serious risk of bias in some critical outcomes.

WHAT'S NEW IN THIS VERSION?

This version includes data from sixteen (16) additional randomized controlled trials. The previously included randomized controlled clinical Phase 3 trial by Dabbous et al. on the efficacy of favipiravir compared to a hydroxychloroquine-based therapy as standard of care was retracted due to questionable reliability of data, hence excluded in this review.

PREVIOUS RECOMMENDATION
As of 08 November 2021

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

Previous 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.

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 December 31, 2022 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 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, hence excluding studies that specifically compared favipiravir with other active treatments or as part of a combination treatment.

RESULTS

Characteristics of included studies

Twenty-two (22) RCTs that included a total of 4,826 adults with RT-PCR confirmed COVID-19 infection ranging from mild to moderate were found. One previously included RCT by Dabbous et al was retracted due to questionable reliability. Fifteen (15) studies included hospitalized adults with newly confirmed COVID-19 infection, while seven (7) RCTs included symptomatic and asymptomatic outpatients who tested positive for COVID-19. Favipiravir was used in different dosing strategies either alone or in combination with standard or supportive care, then compared to standard care or placebo. Seventeen (17) studies did not report vaccination status of participants, with most having recruitment before the worldwide distribution of vaccines. Two (2) studies stated none of their participants received prior COVID-19 vaccination. The remaining three (3) RCTs which reported vaccination status included Chuah et al with only 2 vaccinated participants, Holubar et al with 4 patients who were given at least 1 dose and Lowe et al with 51.2% (n=123) of study participants noted to receive at least 1 dose. Despite having accounted for the vaccination status, the 3 RCTs did not perform subgroup analyses for the critical clinical outcomes being investigated in this review. There were no RCTs found conducted on children or adolescents. The characteristics of the included studies are summarized in Appendix 3.

Certainty of evidence

The overall certainty of evidence was rated moderate due to serious risk of bias and inconsistency in critical outcomes. Thirteen (13) studies had both performance and detection bias due to their open-label nature. The risk of bias summary is in Appendix 4. The GRADE Evidence Summary is in Appendix 5.

Mortality

Favipiravir has no significant benefit on the all-cause mortality of patients with COVID-19 compared to placebo or standard of care (RR 0.98, 95% CI 0.67-1.43, I^2=12%). Subgroup analysis based on hospitalization status showed no significant benefit of Favipiravir on mortality among the inpatients (RR 1.00, 95% CI 0.68-1.46) nor outpatients (RR 0.33, 95% CI 0.01-8.05). A subgroup analysis based on disease severity also showed inconclusive results among those with mild COVID-19 infection (RR 2.89, 95% CI 0.12-69.4) and those with mild and moderate infections (RR 0.98, 95% CI 0.66-1.44, I^2=37%).

Clinical improvement

There is no significant benefit for clinical improvement by day 28 among patients given Favipiravir compared to those given placebo (RR 1.02, 95% CI 0.99-1.05, I^2=2%). A subgroup analysis based on hospitalization showed no significant benefit among the inpatients (RR 1.02, 95% CI 0.98-1.07) nor in the outpatient group (RR 1.01, 95% CI 0.96-1.06). Another subgroup analysis based on disease severity also did not show significant difference among those with mild COVID-19 (RR 0.96, 95% CI 0.45-2.07) nor among those with mild to moderate COVID-19 (RR 1.24, 95% CI 0.90-1.71).

WHO Progression Score Level of 7 or above

Pooled results on clinical deterioration based on the WHO progression score was also inconclusive among patients given Favipiravir (RR 1.30, 95% CI 0.65-2.61, I^2=0%). A similar trend was observed in the subgroup for inpatients (RR 1.23, 95% CI 0.60-2.52, I^2=0%) and outpatients (RR 3.05, 95% CI 0.13-73.39, p=0.49).

Hospitalization

Among outpatients, there was no significant difference in the hospitalization by day 28 among patients given Favipiravir versus the control group (RR 1.03, 95% CI 0.66-1.60, I^2=46%).

Time to recovery

Only one RCT reported time to recovery among inpatients, based on recovery of two or more points on a novel seven-category ordinal scale. There was no significant difference noted between the intervention and control groups (HR 1.03, 95% CI 0.85-1.25, n=446, p=0.73).

Other non-critical outcomes

Incidence of Viral Negative Conversion by Day 7
The pooled risk ratio from eleven studies on the incidence of viral negative conversion was significantly better in the Favipiravir group (RR 1.15, 95% CI 1.05-1.25, I^2=34%). However, on subgroup analysis, the benefit was only seen to be significant among inpatients given Favipiravir (RR of 1.19, 95% CI 1.09-1.31) and not among the outpatient group (RR 1.02 95% CI 0.80-1.29).

Safety

Adverse events were significantly higher among patients given favipiravir compared to those given placebo or standard of care (RR 1.25, 95% CI 1.13-1.38, I^2=70%) with results showing significant heterogeneity. Subgroup analysis show the significantly higher adverse events were noted only among the inpatients given favipiravir (RR 1.48, 95% CI 1.3-1.69, I^2=76%) still with significant heterogeneity; and not among the outpatient population (RR 1.00, 95% CI 0.87-1.16). Adverse events reported include 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]. Gastrointestinal and neurological adverse events were most common in the latest trial by Shah et al [27].

For serious adverse events, patients given favipiravir had no significant difference compared to those given placebo or standard of care (RR 1.13, 95% CI 0.85-1.51, I^2=0%). A subgroup analysis based on hospitalization status likewise did not show significant difference among those in the inpatients (RR 1.14, 95% CI 0.81-1.61) nor among those in the outpatients (RR 1.12, 95% 0.66-1.88). Another subgroup analysis based on disease severity also had no significant difference among those with mild nor mild and moderate COVID-19 infection (RR 1.09, 95% CI 0.71-1.65). Common serious adverse events reported include acute respiratory distress syndrome, death from heart failure, bone fracture, and increasing oxygen desaturation.

RECOMMENDATIONS FROM OTHER GROUPS

Regulatory Agency	Recommendation
NIH COVID-19 Treatment Guidelines (as of November 10, 2022)	No recommendations on the use of favipiravir for the treatment of COVID-19 [8-10].
Surviving Sepsis Campaign Guidelines (as of March 2021)	
Infectious Diseases Society of America (as of June 29, 2022)	
Australian Guidelines for Clinical Care of People with COVID-19 v58.1 (as of November 3, 2022)	Recommends against the use of favipiravir for the treatment of COVID-19 unless in the context of a randomized trial with appropriate ethical approval. Favipiravir should still be considered for other evidence-based indications in people who have COVID-19. Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty, and those receiving palliative care. Until further evidence is available, do not use favipiravir to treat COVID-19 in these populations unless they are eligible to be enrolled in trials [11].
Therapeutics and COVID-19: living guideline (as of September 16, 2022)	No recommendations on the use of favipiravir for the treatment of COVID-1 [22].

ONGOING STUDIES AND RESEARCH GAPS

There are 20 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. All ongoing studies are for adults 18 years old and above and none among children or adolescents. Updates, particularly from the Philippine setting, will be added to this review as soon as results from these trials are available.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

No evidence currently exists on the cost-effectiveness of Favipiravir for COVID-19. Favipiravir (Avigan®) has a cost of US$3 per 200mg tablet (₱150.456). Full treatment course (for longest duration noted) requiring a total of 94 tablets per patient will amount to a total treatment cost of ₱14,100 or US$282 per patient.

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

Favipiravir is currently not FDA approved and, in the Philippines, extreme caution is advised in its use. It is contraindicated in known or suspected pregnancy. Physicians are told to watch out for its possible adverse effects which include: hyperuricemia, diarrhea, neutropenia, and transaminitis. A benefit-risk balance assessment is advised prior to initiation of drug with full disclosure to patients. No evidence is available presently on its ethical, legal, social, and health system impact in the country.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=13/13)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (12)	Uncertain (1)				• Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate (2)	Small (8)	Trivial (2)	Varies	Uncertain (1)	• Favipiravir has no significant benefit on all-cause mortality, clinical improvement, symptom progression, time to recovery, nor hospitalization. • The pooled benefit for the incidence of viral negative conversion is significantly higher for the Favipiravir group (RR 1.14, 95% CI 1.04-1.25, p=0.006).
Harm	Large	Moderate (5)	Small (5)	Trivial (2)	Varies (1)	Uncertain	• The pooled risk of adverse events for patients on Favipiravir was significantly increased (RR 1.25, 95% CI 1.13-1.38, p<0.00001) compared to those given standard of care/placebo. • However, there was no significant difference between those given Favipiravir and standard care/placebo for the risk of serious adverse events (RR 1.09, 95% CI 0.71-1.65, p=0.70).
Certainty of Evidence	High	Moderate (11)	Low (2)	Very low			• Moderate due to serious risk of bias in several critical outcomes.
Balance of effects	Favors intervention	Probably favors intervention (2)	Does not favor intervention or no intervention (3)	Probably favors no intervention (4)	Favors no intervention (2)	Varies (2)	• Favipiravir has no significant benefit on all-cause mortality, clinical improvement, symptom progression, time to recovery, nor hospitalization. • Adverse events were significantly higher in those given Favipiravir but, there was no significant

							difference in serious adverse events between the two groups.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (8)	Probably no important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (7)	Moderate Cost (5)	Negligible cost or savings	Moderate savings	Varies (1)	• Favipiravir (Avigan®) has a cost of US$3 per 200mg tablet (₱150.456). • Full treatment course (for longest duration noted) requiring a total of 94 tablets per patient will amount to a total treatment cost of ₱14,100 or US$282 per patient.
Certainty of evidence of required resources	No included studies (1)	Very low	Low (4)	Moderate (5)	High		
Cost effectiveness	No included studies (3)	Favors using the comparison (3)	Probably favors the comparison (1)	Does not favor either the intervention or the comparison (2)	Probably favors the invention (1)	Varies (3)	
Equity	Uncertain	Varies (4)	Probably reduced (7)	Probably no impact	Probably increased (2)	Increased	
Acceptability	Uncertain	Varies (4)	No (1)	Probably no (3)	Probably yes (5)	Yes	
Feasibility	Uncertain	Varies (2)	No	Probably no (6)	Probably yes (5)	Yes	
Recommendation	For (3)	Against (10)					
Strength	Weak (11)	Strong (2)					

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 December 31, 2022 and Randomized Controlled Trial	December 31, 2022 3:53 PM	14	4
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 December 31, 2022	December 31, 2022 6:00 PM	17	1
COVID-NMA Initiative	Favipiravir	December 31, 2022 8:00 PM	13	12
Google Scholar	Favipiravir AND COVID AND randomized controlled trial	December 31, 2022 9:00 PM	57	10
ClinicalTrials.gov	Favipiravir Filters: Interventional (Clinical Trial), not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, unknown status	December 31, 2022 10:00 PM	52	4
Chinese Clinical Trial Registry	Favipiravir	December 31, 2022 1:30 PM	10	1
EU Clinical Trials Register	COVID-19 AND Favipiravir	December 31, 2022 2:00 PM	12	9

Republic of Korea - Clinical Research Information Service	Favipiravir	December 31, 2022 2:30 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Favipiravir	December 31, 2022 3:00 PM	0	0
CenterWatch	Favipiravir	December 31, 2022 3:30 PM	8	4
chinaxiv.org	Favipiravir	December 31, 2022 4:00 PM	0	0
Medrxiv.org	Favipiravir Filters: March 31, 2021 to May 31, 2022	December 31, 2022 4:30 PM	70	2
Biorxiv.org	Favipiravir Filters: March 31, 2021 to May 31, 2022	December 31, 2022 5:00 PM	97	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

Balykova 2020 [3] (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 [4] (Russia) *Pre-print*	Favipiravir (1800mg bid on day 1, followed by a maintenance dose 800mg bid on days 2-10)	Standard care that included either umifenovir (200 mg 4 qid) + intranasal interferon alpha-2b (10000 IU/ml – 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	RCT Some concerns in the risk of bias	168 hospitalized and outpatient adults (ages 18-60) with mild to moderate PCR-confirmed COVID-19 w/out respiratory failure	<u>Primary</u> Time to clinical improvement (based on a reduction of patient clinical status on at least 1 score according to WHO 8-Category Ordinal Scale for Clinical Improvement compared to screening; Time to viral clearance at day 28 (in 2 negative PCR results) <u>Secondary</u> 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

Bosaeed 2021 [14] (Saudi Arabia)	Favipiravir 1800 mg by mouth BID on day 1 followed by 800 mg BID as a maintenance dose for a total of 5 to 7 days of therapy	Matching placebo	RCT Some concerns in the risk of bias	231 patients (Ages 18 years old and above; median 32-45) from community settings diagnosed with mild COVID-19 (confirmed by positive PCR test for SARS-COV-2) enrolled within 5 days of disease onset	Primary Time to viral clearance (d), median (IQR) Secondary Time to clinical recovery (d), median (IQR); Need to use antibiotics; Complications; Emergency department visits; Hospitalization; ICU admission; Bacterial Pneumonia; 28-day mortality

Chuah 2021 [15] (Malaysia)	Favipiravir 1800 mg BID on day 1 followed by 800 mg BID until day 5 PLUS standard of care	Standard care	RCT Some concerns in the risk of bias	500 hospitalized patients (aged 50 years and above, mean age of 62.5 years) with RT-PCR confirmed COVID-19 infection who had risk factors for disease progression (1 or more known comorbidity for disease progression, hospitalized within the first 7 days from symptom onset, and with mild to moderate clinical severity)	Primary Drop in SpO2 on room air to <95% or requiring supplemental oxygen to maintain SpO2>=95% Secondary Requiring mechanical ventilation; Requiring ICU admission; Died in hospital

Finberg 2021 [16] (USA)	Favipiravir 1800 mg BID on day 1, followed by 1000 mg BID for 13 days	Standard care	RCT Some concerns in the risk of bias	50 hospitalized patients (age 18-80 years) with a SARS-COV-2 PCR-positive nasopharyngeal or oropharyngeal test (within 72 hours of hospitalization and within 7 days of the first positive PCR for SARS-COV-2)	Primary Time to viral clearance Secondary Status of clinical recovery based on the 6-point ordinal scale up to day 60; Time to aggregate NEWS2 score of <=2 or discharge; Total duration of hospitalization

Holubar 2021 [17] (USA)	Favipiravir 1800 mg BID on day 1 then 800 mg BID on days 2-10	Placebo	RCT Low risk of bias	116 asymptomatic or symptomatic outpatients (mean age 43) without respiratory distress with a positive SARS-COV-2 RT-PCR collected within 72 hours of enrollment	Primary Time until shedding cessation of SARS-COV-2 in RT PCR from nasal swabs Secondary Time until: initial symptom resolution, sustained symptom resolution stratified by treatment arm
Pushkar 2020 [18] (Russia)	Favipiravir 1600 mg BID on day 1 then 600 mg BID on days 2-14 of treatment	Standard care according to Russian guidelines that included hydroxychloroquine or chloroquine; or lopinavir/ritonavir	RCT Some concerns in the risk of bias	200 hospitalized patients (Aged 18-80 years of age) diagnosed with SARS-COV-2-infection, with positive RT PCR for SARS COV 2 RNA at screening phase	Primary Rate of clinical status improvement; Time to clinical improvement Secondary Rate of viral elimination by day 10; Time before the end of fever; Rate of transfer to the ICU; Rate of the use of non-invasive lung ventilation; Mortality

Shinkai 2021 [19] (Japan)	Favipiravir 1800 mg BID on day 1 then 800 mg BID on days 2-13 of treatment	Placebo	RCT Some concerns in the risk of bias	156 hospitalized patients (aged 20-74 years) with moderate illness, positive for SARS-COV-2 based on a nucleic acid amplification test of a respiratory tract sample taken at enrollment	Primary Time from study drug initiation to COVID-19 clinical parameter improvement: primary endpoint, temperature, SpO2, Chest imaging, SARS-COV-2 (qualitative) Secondary Adverse events

Shenoy 2021 [20] (Kuwait)	Favipiravir 1800 mg BID on day 1 then 800 mg BID on days 2-10 plus Standard of Care	Placebo plus Standard of Care	RCT Low risk of bias	353 hospitalized patients (aged 21-80 years) tested positive for SARS-COV-2 by real-time RT PCR on a nasopharyngeal or oropharyngeal swab, and clinically assess to have moderate COVID-19 infection	Primary Time to resolution of Hypoxia Secondary Time to hospital discharge; Time to improvement by 1 and by 2 points over baseline in WHO 10-point clinical status score; Proportion of patients who attained WHO 10-point clinical status score improvement by 1 and 2 points; Proportion of patients with disease progression; Summary of deaths recorded in the study by treatment

Lowe 2022 [21] (UK)	Favipiravir 1800 mg BID on day 1 followed by 400 mg four times daily from day 2 to day 7	Placebo	RCT Low risk of bias	240 outpatients(aged 18-70 years) who recently developed COVID-19 symptoms, tested positive for SARS-COV-2 by RT PCR within 7 days of symptom onset or asymptomatic but tested RT PCR positive within previous 2 days (59 patients assigned to Favipiravir+Placebo, 60 assigned to Placebo)	<u>Primary</u> Viral load measured by quantitative PCR performed on saliva samples at Day 5 accounting for the pre-treatment Day 1 viral load <u>Secondary</u> Proportion of participants with undetectable viral loads at Day 5; Rate of decrease in viral load during the 7-day treatment course; Duration of fever; Proportion of participants with medication-related toxicity at Days 7 and 14; Proportion of participants admitted to hospital, intensive care or dead due to a COVID-19 related illness

Rahman 2022 [23] (Bangladesh)	Favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg twice daily from day 2 to day 10	Placebo	RCT High risk of bias	57 inpatients (aged 65-70 years) with respiratory samples tested positive for the novel coronavirus, with initial symptoms presenting within 7 days	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 Secondary - Effect of Favipiravir on hematological and biochemical parameters - Adverse effects on patients of both groups
McMahon 2022 [24] (Australia)	Favipiravir 1800 mg orally twice daily on day 1 followed by 1800 mg twice daily from day 2 to day 14	Placebo	RCT Low risk of bias	200 outpatients (aged 18 years old and above years) with PCR confirmed COVID-19 on nasopharyngeal or combined nose and throat swab, with onset of COVID-19 related symptoms in the prior 5 days	Primary - Time to virological cure (Time Frame: 14 days) - Time to 2 successive throat (or combined nose/throat) swabs negative for SARS-CoV-2 by nucleic acid testing Secondary - All adverse events

Sirijatuphat 2022 [25] (Australia)	Favipiravir 1800 mg orally twice daily on day 1 followed by 800 mg twice daily from day 2 until clinical improvement or saliva RT-PCR became negative (day 5 to 14 days)	Standard of Care	RCT Some concerns in the risk of bias	96 inpatients (aged 18 years or older) with PCR-confirmed SARSCoV-2 infection, with mild to moderate symptoms	Primary - Time to clinical improvement, defined by a National Early Warning Score (NEWS) of ≤1 Secondary - All adverse events

AlQahtani 2022 [26] (Bahrain)	Favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg twice daily from day 2 until day 10	Standard of Care	RCT Some concerns in the risk of bias	106 inpatients (aged at least 21 years) with PCR-confirmed SARSCoV-2 infection, with symptoms requiring admission to hospital	<u>Primary</u> - Clinical scale at end of study follow up (day 14 or on discharge/death, whichever is earlier) <u>Secondary</u> - Viral clearance - Discharge and length of hospital stay - 30 days readmission rate - 30 days mortality rate - Daily Sequential Organ Failure Assessment (SOFA) score - Daily National Early Warning Score (NEWS) 2 score - Requirement of escalation of respiratory support - Clinical improvement defined as patient discharge or a reduction of 2 points on a 6-point disease severity clinical scale - Need of ICU care - Adverse events - Change in laboratory measures (C reactive protein, lactate dehydrogenase, ferritin, D-dimer and lactate)

Shah 2022 [27] (UK)	Favipiravir 1800 mg orally twice daily on day 1 followed by 800 mg twice daily for 9 days AND standard care	Standard of Care alone	RCT Some concerns in the risk of bias	499 inpatients (aged older than 18 years) with PCR-confirmed SARSCoV-2 infection, with symptoms requiring admission to hospital	Primary - Time from randomisation to recovery of two or more points on the seven-category ordinal scale or discharge from the hospital Secondary - All-cause mortality - Requirement for intensive care admission or ventilatory support - Readmission rates - Change in clinical status from randomization to 28 days after randomization
Adhikari 2022 a [28] (Nepal)	Favipiravir 1800 mg orally twice daily on day 1 followed by 800 mg twice daily from day 2 until day 5	Placebo	RCT Some concerns in the risk of bias	70 inpatients (aged 18 - 80 years) with PCR-confirmed SARSCoV-2 infection, with mild COVID-19 infection	Primary - Clinical improvement

Golan 2022 [29] (USA, Brazil, Mexico)	Favipiravir 1800 mg orally twice daily on day 1 followed by 800 mg twice daily from day 2 until day 10	Placebo	RCT Some concerns in the risk of bias	1211 outpatients (aged 18 years or older) with PCR-confirmed SARS CoV-2 infection, with mild to moderateCOVID-19 infection	Primary - Time to Sustained Clinical Recovery
Tehrani 2022 [30] (Iran)	Favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg twice daily for the next 4 days	Standard of Care	RCT Some concerns in the risk of bias	78 outpatients (aged 18 years or older) with PCR-confirmed SARS CoV-2 infection, with moderateCOVID-19 infection	Primary - Hospitalization rate during the seven-days follow-up period

Appendix 4: Study Appraisal

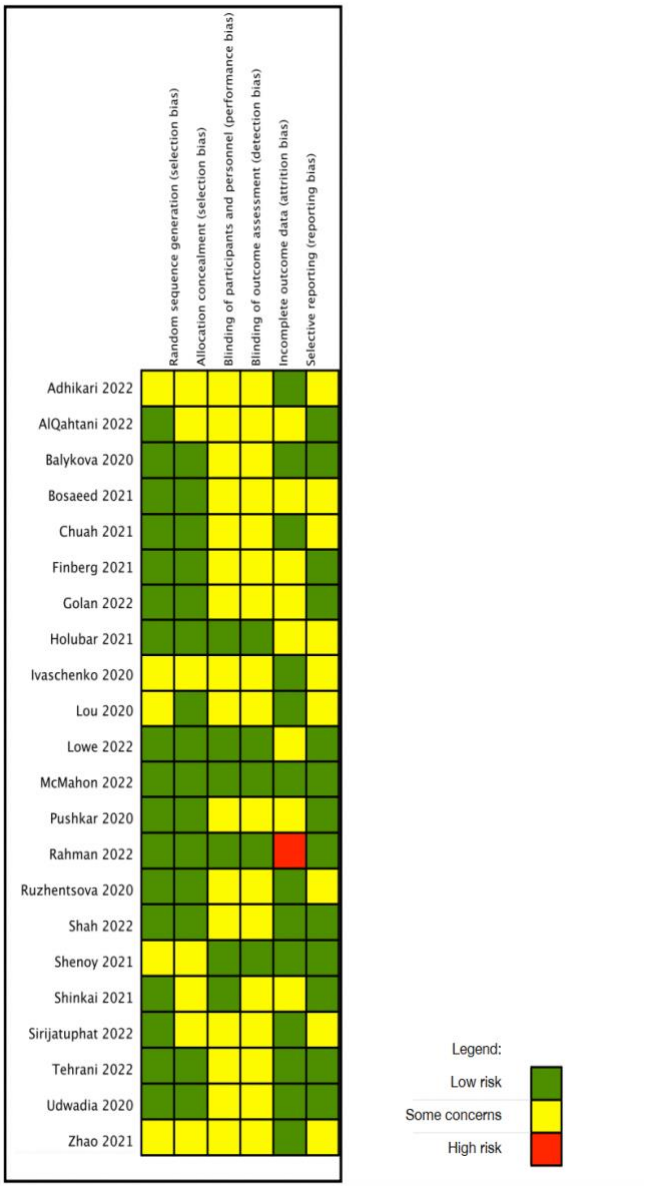

Figure 1. Risk of Bias Summary for Included Studies

Appendix 5: GRADE Evidence Profile

Author(s): Christdianzen Grace P. Saroca, MD
Question: Favipiravir compared to Standard of Care/Placebo for COVID-19 infection
Setting: Worldwide

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Standard of Care/Placebo	Relative (95% CI)	Absolute (95% CI)		
All cause mortality (follow-up: range 14 days to 30 days)												
19	randomised trials	serious [a]	not serious	not serious	not serious	none	46/2224 (2.1%)	47/2087 (2.3%)	**RR 0.98** (0.67 to 1.43)	**0 fewer per 1,000** (from 7 fewer to 10 more)	⨁⨁⨁◯ Moderate	CRITICAL
Clinical Improvement by Day 28												
14	randomised trials	serious [b]	not serious	not serious	not serious	none	1219/1518 (80.3%)	1120/1427 (78.5%)	**RR 1.02** (0.99 to 1.05)	**16 more per 1,000** (from 8 fewer to 39 more)	⨁⨁⨁◯ Moderate	CRITICAL
WHO Progression Score level 7 or above at day 28												
8	randomised trials	not serious	serious [c]	not serious	not serious	none	16/656 (2.4%)	11/652 (1.7%)	**RR 1.30** (0.65 to 2.61)	**5 more per 1,000** (from 6 fewer to 27 more)	⨁⨁⨁◯ Moderate	CRITICAL
Hospitalization at Day 28 among Outpatients												
4	randomised trials	serious [d]	not serious	not serious	not serious	none	31/393 (7.9%)	31/397 (7.8%)	**RR 1.03** (0.66 to 1.60)	**2 more per 1,000** (from 27 fewer to 47 more)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of Viral Negative Conversion by day 7												
11	randomised trials	serious [d]	not serious	not serious	not serious	none	406/648 (62.7%)	302/576 (52.4%)	**RR 1.15** (1.05 to 1.25)	**79 more per 1,000** (from 26 more to 131 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Adverse events (follow-up: range 28 days to 30 days)												
16	randomised trials	serious [d]	serious [e]	not serious	not serious	none	639/2174 (29.4%)	430/2010 (21.4%)	**RR 1.25** (1.13 to 1.38)	**53 more per 1,000** (from 28 more to 81 more)	⨁⨁◯◯ Low	IMPORTANT
Serious Adverse events (follow-up: range 14 days to 60 days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Standard of Care/Placebo	Relative (95% CI)	Absolute (95% CI)		
16	randomised trials	serious [d]	not serious	not serious	not serious	none	88/1958 (4.5%)	75/1782 (4.2%)	**RR 1.13** (0.85 to 1.51)	**5 more per 1,000** (from 6 fewer to 21 more)	⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. Issues on selection, performance, detection, and reporting bias.
b. Issues on performance, detection and attrition bias.
c. Issues on attrition bias.
d. Issues on selection, performance, detection, attrition, and reporting bias.
e. High heterogeneity at I2=75%.

Appendix 6: Forest Plots

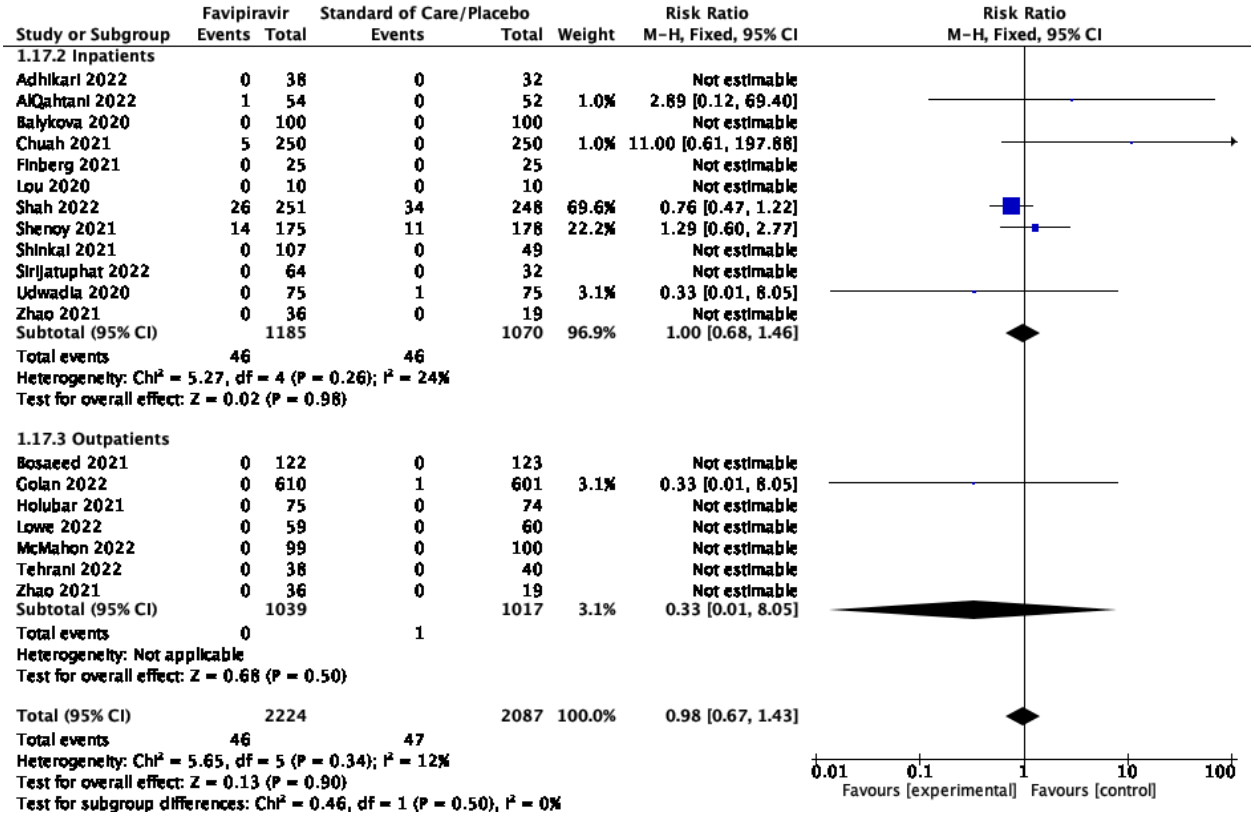

Figure 2. All-cause mortality (Day 14-30) with subgroup analysis of inpatients and outpatients

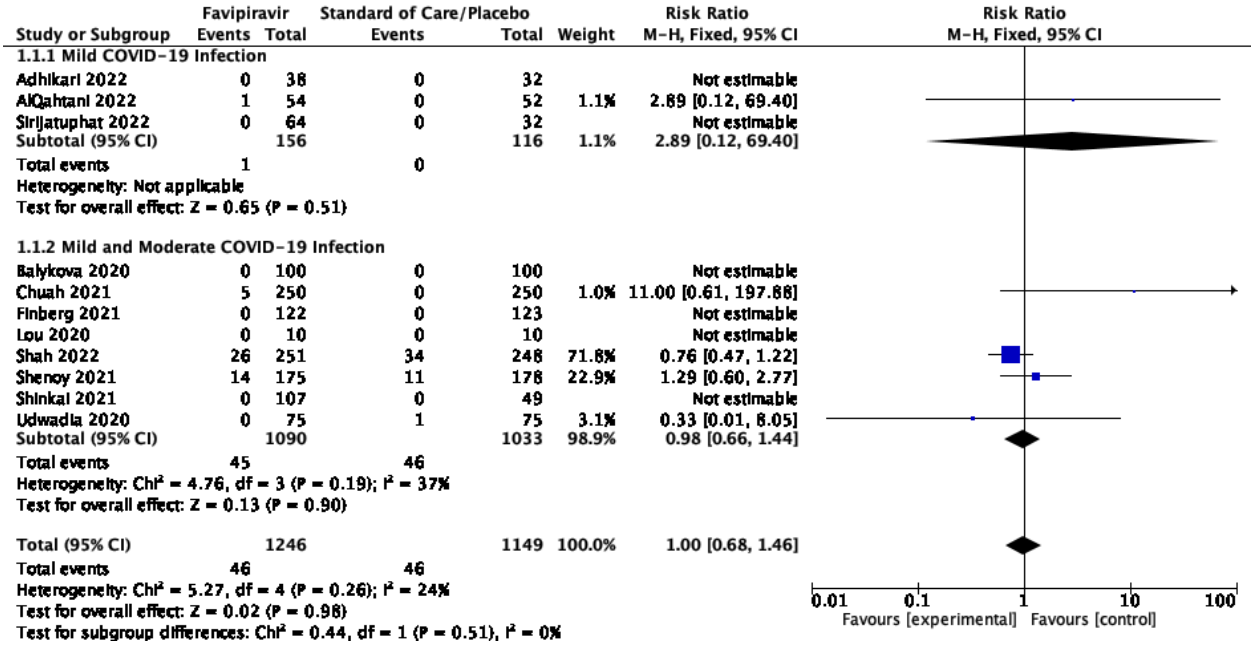

Figure 3. All-cause mortality (Day 14-30) with subgroup analysis among inpatients for Mild and Mixed infections

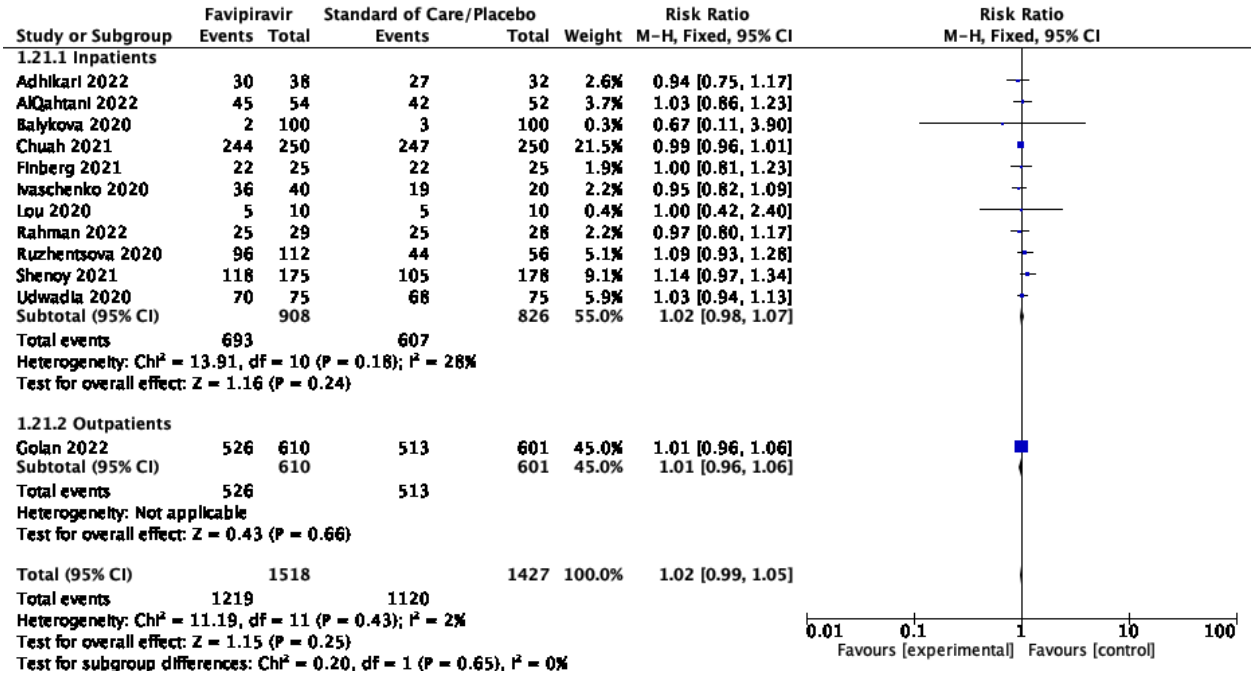

Figure 4. Clinical Improvement by Day 28 with subgroup analysis of inpatients and outpatients

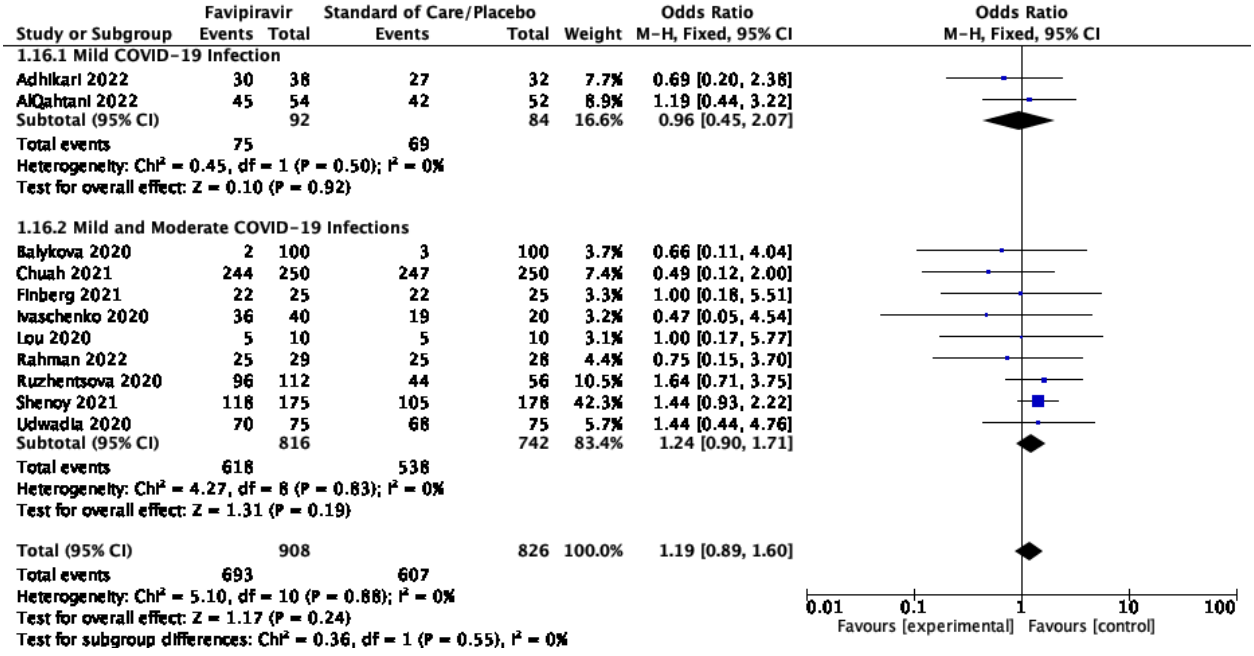

Figure 5. Clinical Improvement by Day 28 with subgroup analysis among inpatients for Mild and Mixed infections

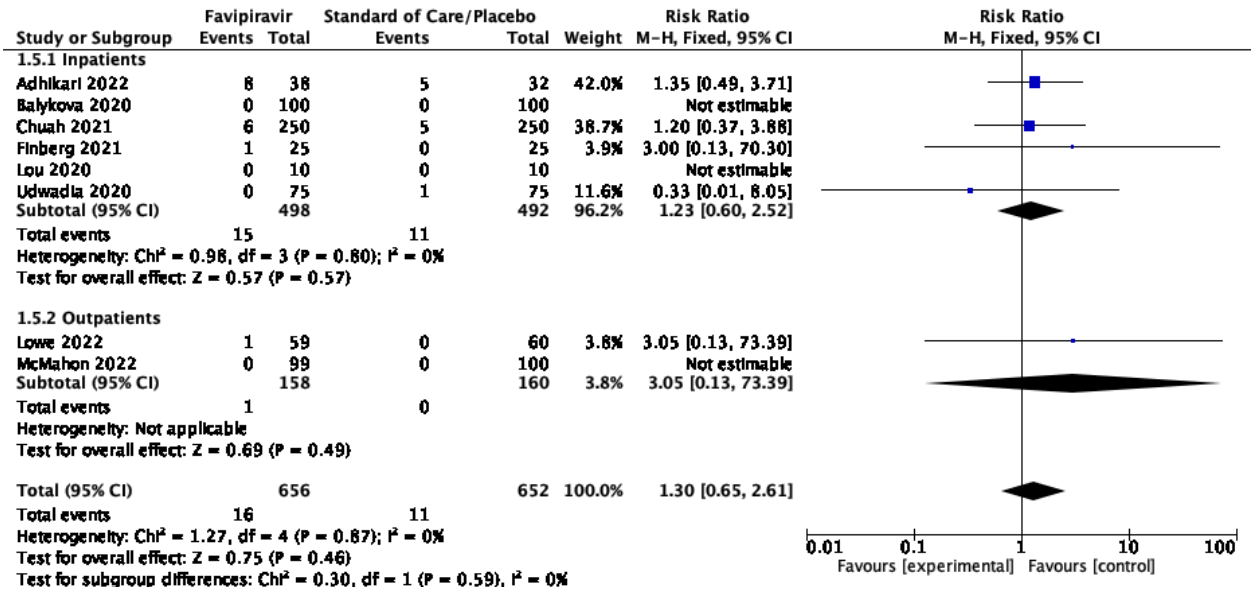

Figure 6. WHO Progression Score Level 7 or above with subgroup analysis of inpatients and outpatients

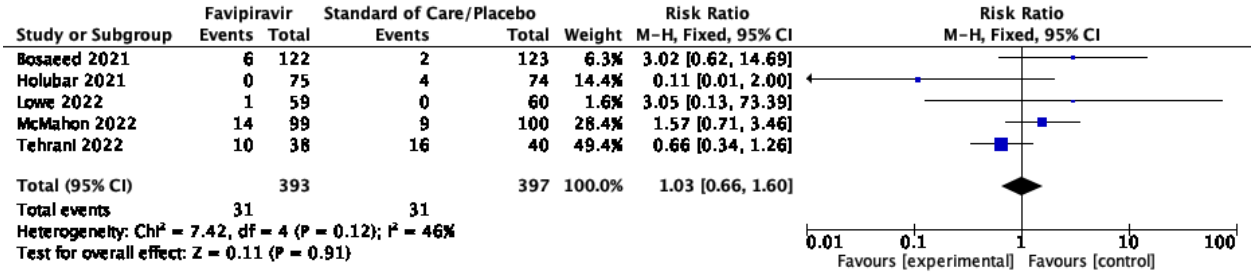

Figure 7. Hospitalization among Outpatients

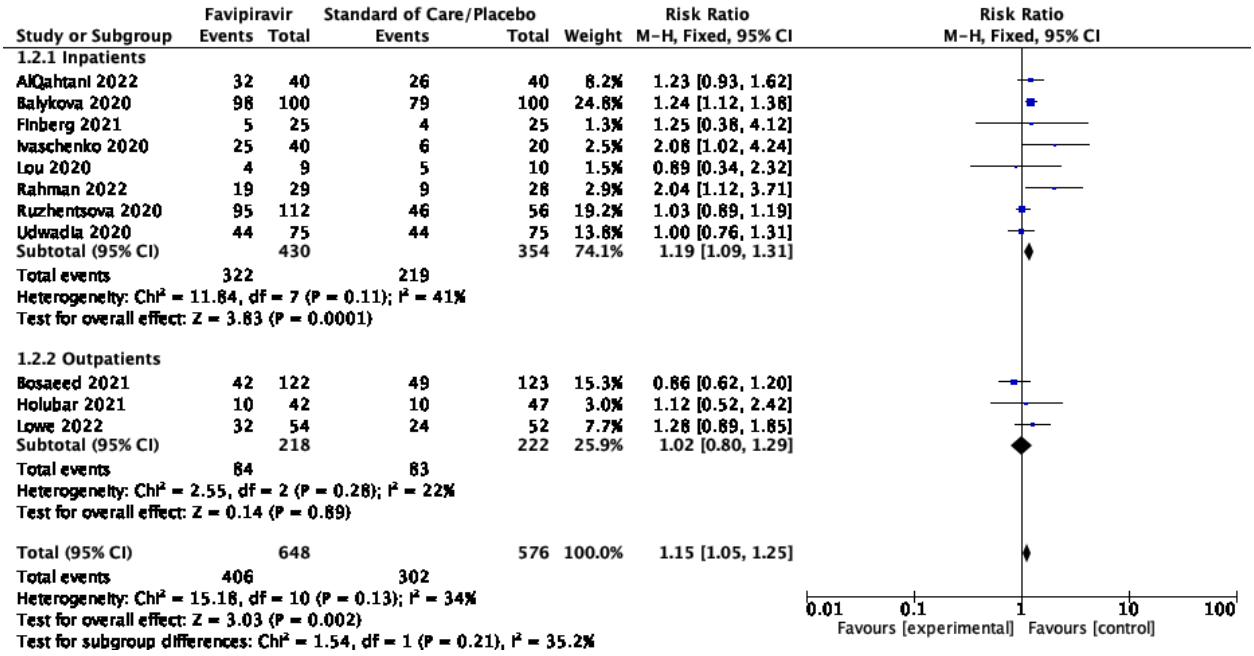

Figure 8. Incidence of Viral Negative Conversion by Day 7 with subgroup analysis of inpatients and outpatients

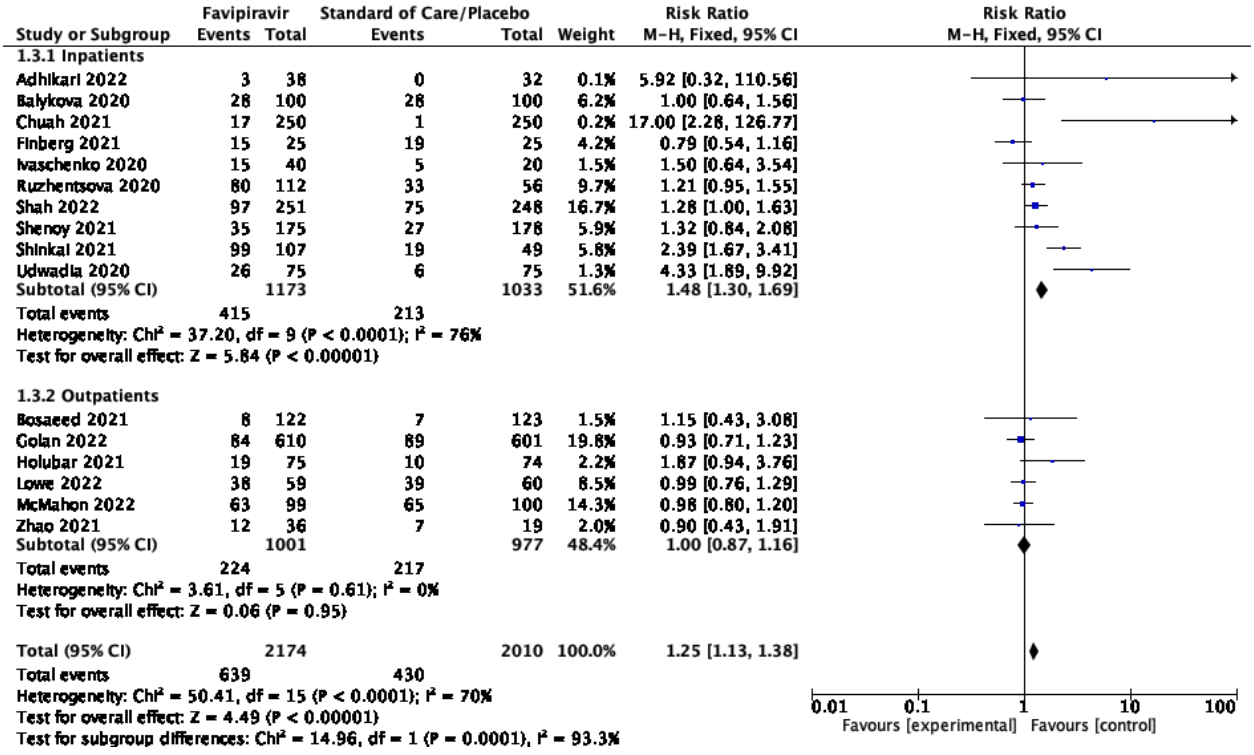

Figure 9. Adverse events at day 28-30 with subgroup analysis of inpatients and outpatients

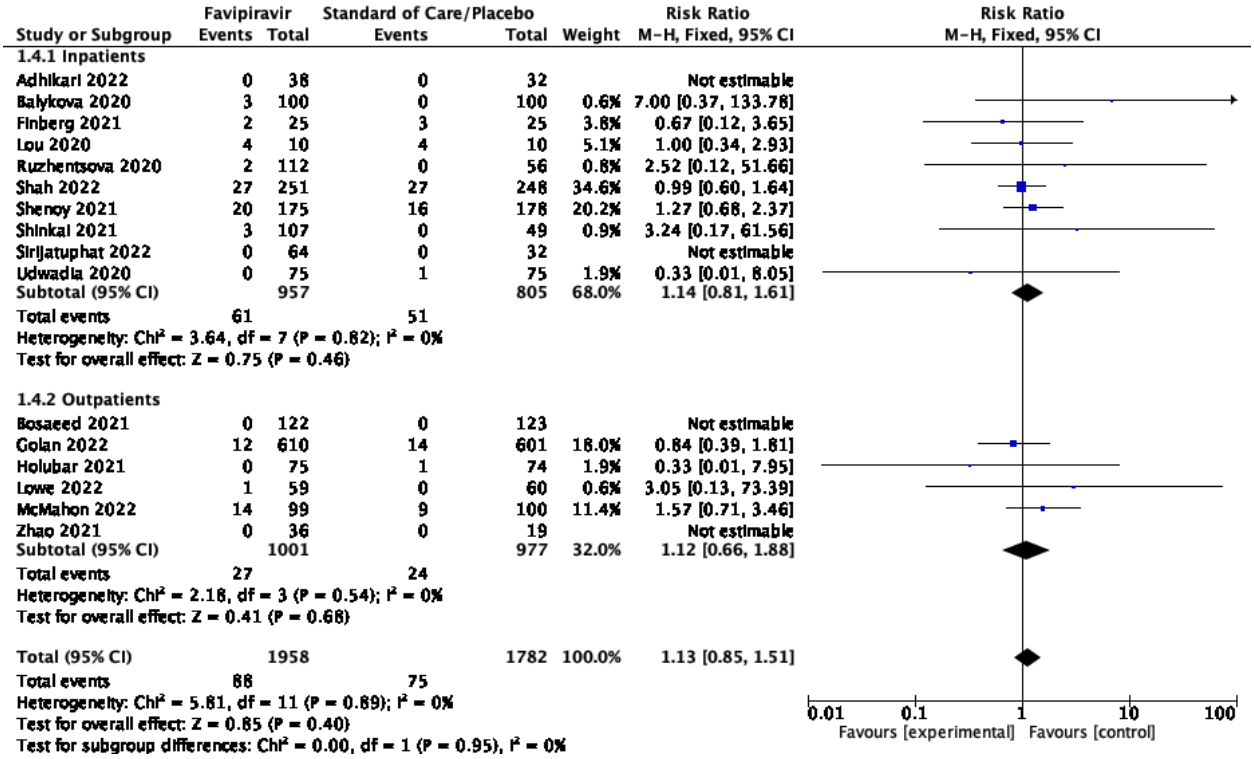

Figure 10. Serious Adverse events with subgroup analysis of inpatients and outpatients

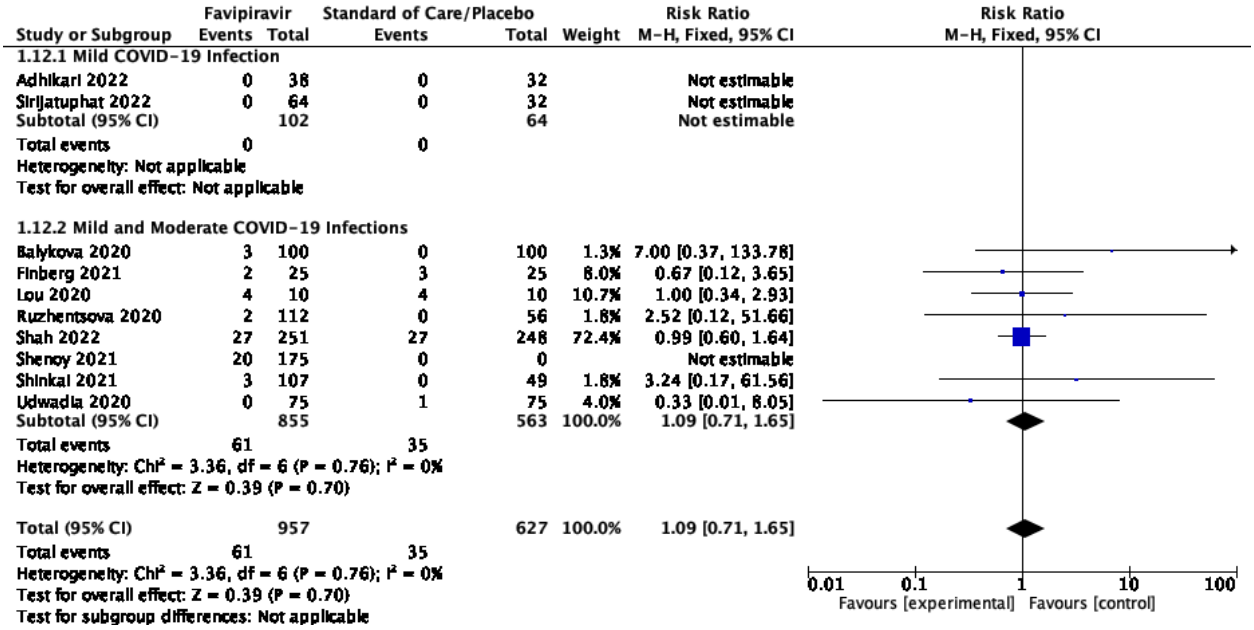

Figure 11. Serious Adverse events among inpatients for Mild and Mixed infections

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 Study To Evaluate The Performance And Safety Of Favipiravir in CO VID-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

5. 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
6. 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) *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)	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
7. 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
8. 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

9. 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
10. 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
11. 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 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.	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

12. 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
13. 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
14. 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
15. 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

16. 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) Control: No treatment (except antipyretics – paracetamol)	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
17. 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
18. 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
19. 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

20. 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