EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

FAVIPIRAVIR FOR THE TREATMENT OF COVID-19

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V 5.0	**13/12/2020**	Fifth version
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V 7.0	**15/02/2021**	Seventh version

Major changes from previous version

Chapter, page no.	***Major changes from version 6.0***
Summary, 13-14 **Table 4-42, 74**	The pool of included studies has changed. The following ongoing trials were added: • One phase two RCT (NCT04718285, n=380)
Table 4-17, 44 to Table 4-42, 74	Actual status of all ongoing trials listed in Tables 4 are verified and updated when indicated.
Appendix Table 6-2, 81	The search strategy for observational studies has changed

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
AZ	azithromycin
BID	Twice daily
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
FV	favipiravir
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HQ	hydroxychloroquine
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ID	Identifier
ITT	Intention-to-treat
L/R	Lopinavir/ritonavir
MD	Mean Difference
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Not applicable
NR	Not reported
OR	Odds Ratio
po	Per os (oral administration)
PP	Per Protocol
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
TID	Three times daily
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Favipiravir, a broad-spectrum antiviral treatment. The mechanism of action of favipiravir is the selective inhibition of RNA polymerase by favipiravir ribosyl triphosphate formed by cellular enzymes in the influenza virus leading to antiviral activity. Favipiravir is principally used as treatment during outbreak of novel or re-emerging influenza virus infections in which other influenza antiviral drugs are either not effective or insufficiently effective.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis.

The sources and search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Favipiravir, a broad-spectrum antiviral treatment. The mechanism of action of favipiravir is the selective inhibition of RNA polymerase by favipiravir ribosyl triphosphate formed by cellular enzymes in the influenza virus leading to antiviral activity. Favipiravir is principally used as treatment during outbreak of novel or re-emerging influenza virus infections in which other influenza antiviral drugs are either not effective or insufficiently effective.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).
One researcher from SNHTA extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25). For prospective single arm studies, the checklist for prevalence studies of the Johanna Briggs Institute is used to assess the methodological rigor and applicability [4].

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/
- International Clinical Trials Registry Platform (ICTRP): https://clinicaltrials.gov/ct2/who_table

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of SNHTA is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com & scholar.google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Favipiravir is a broad-spectrum antiviral treatment. The mechanism of action of favipiravir is the selective inhibition of RNA polymerase by favipiravir ribosyl triphosphate formed by cellular enzymes in the influenza virus leading to antiviral activity. Favipiravir was initially intended for the treatment of RNA viruses such as Ebola and Influenza [5].

3.2 Regulatory Status

Favipiravir (ATC-code J05AX27) is marketed by Appili Therapeutics (Japan) under the brandname Avigan®. The Marketing Authorisation holder (MAH) is FUJIFILM Toyama Chemical Co., Ltd, the market authorisation was granted in 2014 by Japan for the treatment of new emerging influenza. The drug is to be considered for use only when there is an outbreak of novel or re-emerging influenza virus infections in which other influenza antiviral drugs are either not effective or insufficiently effective [6, 7].

Favipiravir had not been approved for marketing in any countries other than Japan, until March 2020, when China approved it for the treatment of COVID-19. In June 2020, India approved favipiravir under the brandname Fabiflu manufactured by Glenmark. As of today, favipiravir remains unapproved in Europe and the USA, but the US Food and Drug Administration (FDA) granted clearance to an investigational new drug (IND) application for favipiravir so that Appili can proceed with phase-2 / 3 clinical trials evaluating the efficacy and safety of favipiravir for the treatment and prevention of COVID-19.

The patent of the compound of this agent expired in 2019, so that other manufacturers can produce the generic drug favipiravir, which is now sold under the brand names Avigan, Abigan, Avifavir, Areplivir, FabiFlu, and Favipira.

3.3 Level of Evidence

The flow diagrams depict the screening process to identify eligible studies (Appendix Figure 6-1, Appendix Figure 6-2).

Detailed description to ten included RCTs can be found in Table 4-9 to Table 4-14. The outcome data from these trials are included in Summary of Findings Table 4-1 to Table 4-8.

Favipiravir versus standard care

Six RCTs are summarised in the Summary of Findings Table 4-1 [8-13].

A small 3-arm controlled trial randomized 30 Chinese hospitalized patients in a 1:1:1 ratio into a baloxavir marboxil group, a favipiravir group, and a control group [10]. Standard care was provided in all groups,

including the administration of Lopinavir / Ritonavir or Darunavir / Cobicistat and Umifenovir, in combination with interferon-α. The primary outcome was the percentage of subjects with viral negative by Day 14 and the time from randomization to clinical improvement. Trial descriptions can be found in Table 4-9.

An interim report to a phase 2/3 3-arm RCT conducted in Russia is included in the Summary of Finding table (Table 4-1) [9]. The trial compared two dosing schedules of favipiravir (avifavir) versus standard of case in 60 hospitalized adult patients with moderate COVID-19 (NCT04434248). Avifavir schedule was either 1600 mg twice daily (bid) on day 1, followed by 600 mg bid on day 2 to 14 or avifavir 1800 mg bid on day 1 followed by 800 mg bid on days 2 to 14. WHO ordinal scale for clinical improvement, PCR for SARS-Cov-2 detection (viral clearance) and daily vital signs are measured up to day 10. Another RCT was conducted in Russia, sampling both hospitalised patients and outpatients with mild to moderate COVID-19 without respiratory failure [11]. Favipiravir plus standard care was provided to 112 patients, with a dose of 1800mg twice daily on day one, followed by 800mg on day 2 to 10. Fifty-six patients received standard care only. Primary outcomes were time to clinical improvement and time to viral clearance up to day 28. Outcome data from a third trial conducted in Russia was added to the Summary of Finding Table 4-1 [13]. The study with identifier NCT04542694 has posted study results and the statistical analyses plan on the clinicaltrials.gov website, and was recently published in Russian [13]. This two-arm randomised open label trial compared Areplivir plus standard of care with standard of care alone in 200 hospitalized patients. Four patients in the areplivir group did not complete the intervention, two due to the need of therapy that was not allowed by protocol, one was withdrawn due to an adverse event and 1 because of a protocol violation. Nobody dropped out of the standard of care trial arm. Areplivir was provided at a dose of 1600 mg twice daily on day 1, followed by 600 mg daily on day 2 to 14. Standard of care might include hydroxychloroquine with or without azithromycin, chloroquine, lopinavir/ritonavir or other recommended schemes that are approved by the Russian Ministry of Health. Participants had a mean age of 49.7 years.

One trial was conducted in Egypt and included patients with mild to moderate COVID-19 [8]. Fifty patients were randomised to favipiravir and 50 to hydroxychloroquine plus oseltamivir. The favipiravir dose was 3200 mg at day1, followed by 600 mg twice on day2 to day 10). The hydroxychloroquine dose was 800 mg at day1 followed by 200 mg twice on day2 to 10. Oseltamivir was provided orally with 75mg each 12 hours per day for 10 days. The primary endpoints consisted of viral clearance, normalization of body temperature for 48 hours, improvement of radiological abnormalities at day 14 and discharge rate out of the hospital. Methodologic features of these trials are addressed in Table 4-1 and Table 4-9.

One RCT was conducted in India, in 150 patients with mild to moderate COVID-19 [12]. Favipiravir plus standard care was provided to 75 patients, standard care alone in 75 patients. The dosing was 1800 mg twice daily on day 1, followed by 800 mg twice daily on day 2 to 14. The primary outcome was time to cessation of the SARS-CoV-2 virus. The description of standard care provided in the trial is found in Table 4-10.

Favipiravir versus specific agents

Four RCTs have been published comparing favipiravir with other active agents [10, 14-16].

One RCT compared favipiravir with Umifenovir (arbidol) in a Chinese population [14]. Trial descriptions can be found in Table 4-2, Table 4-11 and Table 4-29. On day 1, the dose of favipiravir was 1600 mg twice daily, and 600 mg twice daily on day 2 to 7. Arbidol was provided 3 times daily in a dose of 200mg (total of 600 mg daily) from day 1 to end of trial. Treatment duration was 7 to 10 days. Except arbidol and favipiravir, some other drugs were provided for conventional therapy. The primary outcome in latter trial was the clinical recovery rate at 7 days or the end of treatment.

An interim analyses to another RCT was identified, of which no trial registration was found [15]. The trial planned to enrol 190 hospitalized adults with moderate to severe COVID-19 pneumonia, but due to logistical and financial constraints, 89 were randomised. This open label two-arm RCT was conducted in Oman and compared oral favipiravir with interferon beta-1b by inhalation aerosol against hydroxychloroquine (HCQ). Mean age of participants was 55 years. The primary outcome were time from assignment to clinical recovery, the normalization of inflammatory markers and improvement in oxygen saturation that is maintained for at least 72 hours (Table 4-12).

Another Chinese trial is described in Table 4-4, Table 4-5, Table 4-6, and Table 4-13. This three-arm multicentre open label trial compared favipiravir + standard care with either Favipiravir + Tocilizumab or with Tocilizumab alone [16]. For completeness, all three possible comparisons are described in this report. Favipiravir was provided 1600 mg twice daily on day 1, followed by 600mg twice daily on day two to seven. The first dose of Tocilizumab was 4 ~ 8 mg/kg and the recommended dose was 400 mg. Primary outcome described in the published report was the cumulative lung remission rate. At the trial registration site, a different primary outcome was listed (Table 4-13).

The fourth trial concerned a three-arm trial comparing Favipiravir versus Baloxavir and favipiravir versus standard dare in Chinese patients [10]. This trial is described above under the heading “Favipiravir versus standard care” and in Table 4-9.

Early versus late Favipiravir

We identified one Japanese trial comparing early with late favipiravir treatment (Table 4-8, Table 4-14) [17]. Outcome data was published in a peer reviewed journal but was also uploaded to the registration site [18]. This multicenter, open-label, randomized clinical trial evaluated immediate treatment with favipiravir (Avigan) on day 1 with a delayed scheme on day 6. The study population consisted of 89 persons who were asymptomatic or mildly ill with SARS-CoV2 infection. The primary endpoint was viral clearance by day 6. For the SARS-Cov-2 clearance outcomes, eight patients in the early favipiravir arm and 11 in the late favipiravir arm were excluded, as these had a negative PCR on day 1. Standard of care was not detailed, but concomitant therapy was described. Eight out of 44 (18.2%) in the early treatment group received systemic antibodies compared to 3 out of 44 (6.8%) in the late treatment group. Systemic corticosteroids were given in 2 patients (4.5%) in the early treatment group and in no patient of the late treatment group. Nobody received other antiviral agents or antiplatelet or antithrombotic agents.

Observational studies

Appendix Figure 6-2 shows the selection process for observational studies, resulting in the inclusion of three studies [19-21]. No additional study was identified in this update. Table 4-15 and Table 4-16 describe safety outcomes for Favipiravir as reported in the Japanese, Chinese and Turkish observational studies [19-21]. The Turkish study had a 3-arm non-randomised comparative design evaluating favipiravir with hydroxychloroquine (HQ) with or without azithromycin (AZ) [20]. The Chinese study had a controlled before-after design comparing favipiravir with Lopinavir/ritonavir [19]. The Japanese trial was a large prospective multicentre uncontrolled observational study enrolling 2158 hospitalised patients with mainly mild to moderate Covid-19 [21]. Avigan was provided for a median of 11 days, with a typical loading dose of 1800 mg twice on day 1, followed by 800 mg bid on subsequent days (Table 4-16). Concomitant use of Ciclesonide, an inhaled steroid agent, was provided in 41.6% of patients, Lopinavir-ritonavir in 3.4%. Twenty-eight percent of patients received other COVID-19 related therapy, which was not further specified. The dose schedule of favipiravir provided was similar across all observational studies.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Favipiravir versus standard care

Six RCTs contributed to the estimates presented in the Summary of Findings Table. The certainty of the evidence was low to very low for each of the outcomes listed in the Table. It is unclear if favipiravir reduces all-cause mortality in hospitalised patients (RR 0.56; 95% CI 0.09 to 3.51; very low certainty evidence). In absolute terms, this translates to 3 fewer death per 1.000 (95% CI from 7 fewer to 20 more, Table 4-1).

Favipiravir may have a small effect on the number of patients discharged from hospital at day 15 (RR 1.11, 95% CI 0.91 to 1.35; low certainty evidence) while it does not seem to increase the SARS-CoV-2 clearance up to 14 days importantly (RR 1.04, 95% CI 0.94 to 1.15; low certainty evidence). Time to SARS COV-2 clearance in in- and outpatients may be shorter in favipiravir when compared to standard care (HR: 1.32, 95% CI 1.03 to 1.69; low certainty evidence). The certainty of the other four outcomes in the Summary of Findings Table 4-1 was of very low certainty, so that it is currently unclear whether favipiravir affects the number of patients with respiratory failure and respiratory distress syndrome, progression of COVID-19 disease or the number of patients with serious adverse events, when compared to standard care. Additional patient relevant outcomes are reported in the six studies, which are summarised in Appendix Table 6-4.

Due to the low to very low certainty of the evidence for the comparison favipiravir compared to standard care, we conclude that favipiravir may have small effects on hospital discharge up to day 15 and may reduce the time to viral clearance, but effects on other important outcomes remain unclear. The current evidence base is insufficient to support the use of favipiravir for patient with mild to severe COVID-19. No trial was identified that evaluated favipiravir in patients with critical COVID-19.

Favipiravir versus Umifenovir

The Chinese trial was too small to evaluate effects of favipiravir on all-cause mortality, no death occurred in either trial arm during the relative short follow-up duration [14]. When compared to umifenovir, favipiravir may increase the number patient with adverse events, but the evidence is of low certainty. The single trial that contributed to this comparison, did not report other outcomes of interest to this report.

The current evidence base does not support the use of favipiravir in combination with other medicines for the treatment of mild to moderate COVID-19.

Favipiravir + interferon beta1b versus Hydroxychloroquine

The certainty of the evidence from the single study contributing to this comparison was very low. As a consequence, it is unclear if favipiravir + interferon beta1b has a positive effect on all-cause mortality at day 14, the number of patients discharged at day 14, admissions to ICU or the length of hospital stay, when compared to hydroxychloroquine (Table 4-3).

Favipiravir versus Tocilizumab

The certainty of the evidence from the single study contributing to this comparison was very low [16]. As a consequence, it is unclear whether favipiravir affects the number of patients with significant improvement in lung disease on CT, the number of patients with serious adverse events, or the number of patients with any adverse event (Table 4-4, Table 4-13).

Favipiravir + Tocilizumab versus Tocilizumab

The certainty of the evidence from the single study contributing to this comparison was very low [16]. As a consequence, it is unclear whether favipiravir + tocilizumab when compared to tocilizumab alone affect the number of patients with significant improvement in lung disease on CT, the number of patients with serious adverse events, or the number of patients with any adverse event (Table 4-5, Table 4-13).

Favipiravir + Tocilizumab versus Favipiravir

The certainty of the evidence from the single study contributing to this comparison was very low [16]. As a consequence, it is unclear whether favipiravir + tocilizumab when compared to favipiravir alone affect the number of patients with significant improvement in lung disease on CT, the number of patients with serious adverse events, or the number of patients with any adverse event (Table 4-6 and Table 4-13).

Favipiravir versus Baloxavir

The certainty of the evidence from the single study contributing to this comparison was very low [10]. As a consequence, it is unclear if favipiravir, when compared to baloxavir, increases SARS-CoV-2

clearance up to 14 days, reduces the number of patients with respiratory failure and respiratory distress syndrome or affects all-cause mortality (Table 4-7).

Early versus late favipiravir

The Japanese trial was too small to evaluate effects of favipiravir on all-cause mortality (Table 4-8)[17, 18]. No death occurred in either trial arm during the course of the study and none of the participants experienced progression of the COVID-19. It is unclear if early favipiravir reduces the time to viral clearance (HR 1.42, 95% CI 0.76 to 2.62, very low certainty evidence, HR above 1 indicating favouring early favipiravir). When compared to delayed provision of favipiravir, immediate provision of favipiravir may positively affect time to hospital discharge (1.96, 95% CI 1.33 to 2.89, low certainty evidence). Although limited, the currently available evidence may suggest to favour early favipiravir over late favipiravir for time to hospital discharge. The evidence however needs to be interpreted along with the evidence comparing for example favipiravir versus standard of care. As all other ongoing and completed trials compare favipiravir on day 1 versus standard care or other active agents, the evidence on early versus late favipiravir treatment will unlikely be revisited.

4.2 Safety evidence from observational studies

The large uncontrolled study in Japan reported adverse events possibly or likely related to favipiravir in 532 out of 2158 patients (24.7%) [21]. Most frequent adverse events were hyperuricemia in 335 (15.5%) and liver injury or liver function test abnormalities in 159 (7.4%) patients. The study used survey methods to collect safety data from 407 participating hospitals and performed minimal data cleaning. The study design was not well described, so that the risk of bias at study and outcome level is unclear. The two smaller controlled studies at high risk of bias reported on few safety outcomes. Patients with any adverse events was reported in one study, where 4 out of 35 (11.4%) adverse events occurred in the favipiravir group and in 25 out of 45 (55.56%) of the Lopinavir/ritonavir group. In the two studies with control group, none of the patients was withdrawn because of adverse events in either arm. The two small case series provided little additional evidence.

4.3 Ongoing studies

Table 4-17 to Table 4-41 describe ongoing trials for favipiravir of any brandname. In this update, we added descriptions to 1 ongoing phase 2 study.
Overall, 54 ongoing RCTs are included, of which 18 evaluate favipiravir in combination with another pharmacotherapy. The remainder evaluate favipiravir as single agent in addition to standard of care. The publication of safety outcomes from four ongoing observational studies are awaited.

4.4 Scientific conclusion about status of evidence generation

The current evidence base does is not sufficient to support the use of favipiravir as monotherapy or combination therapy for COVID-19.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Favipiravir versus standard care

Patient or population: COVID-19 infection
Setting: Hospital inpatients and outpatients
Intervention: Favipiravir & standard care[a]
Comparison: Standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with standard care	Risk with favipiravir				
All-cause mortality *Inpatients*	8 per 1000	4 per 1000 (1 to 28)	RR 0.56 (0.09 to 3.51)	3 fewer per 1.000 (from 7 fewer to 20 more)	527 (5[b]) [8-10, 12, 13]	very low[c,d]
Number of patients discharged up to day 15 *Inpatients*	790 per 1000	877 per 1000 (719 to 1000)	RR 1.11 (0.91 to 1.35)	87 more per 1.000 (from 71 fewer to 276 more)	407 (2[b]) [9, 12, 13]	low[e,f]
SARS-CoV-2 clearance, 7 to 14 days *Inpatients & outpatients*	823 per 1000	856 per 1000 (774 to 947)	RR 1.04 (0.94 to 1.15)	33 more per 1.000 (from 49 fewer to 123 more)	494 (6[b]) [8-13]	low[f,g]
Time to SARS COV-2 clearance *Inpatients & outpatients*	HR: 1.32 (1.03 to 1.69)			-	299 (2)[11, 12]	low[h,i]
Number of patients with respiratory failure and respiratory distress syndrome *Inpatients*	400 per 1000	444 per 1000 (156 to 1000)	RR 1.11 (0.39 to 3.19)	44 more per 1.000 (from 244 fewer to 876 more)	19 (1) [10]	very low[d,j]
Progression of COVID-19 disease: *transfer to ICU, inpatients & outpatients*	6 per 1000	10 per 1000 (1 to 90)	RR 1.50 (0.16 to 14.09)	3 more per 1.000 (from 5 fewer to 84 more)	368 (2) [11, 13]	very low[d,h]
Progression of COVID-19 disease: *Hospitalisation, outpatients*	45 per 1000	43 per 1000 (35 to 52)	RR 0.94 (0.78 to 1.14)	3 fewer per 1.000 (from 10 fewer to 6 more)	168 (1) [11]	very low[d,h]
Number of patients with serious adverse events *Inpatients & outpatients*	21 per 1000[k]	27 per 1000 (11 to 67)	RR 1.29 (0.52 to 3.20)[k]	6 more per 1000 (from 10 fewer to 46 more)	332 (4) [10-13]	very low[d,k,l]

Source: Outcome data from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [22], GRADE assessment adapted from covid-nma.com or assessed by SNHTA if absent in covid-nma; descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA), estimates on the outcome *serious adverse events* & *Progression of COVID-19 disease: Hospitalisation, outpatients* added by SNHTA.
Abbreviations: CI: Confidence interval; RR=relative risk; HR=hazard ratio
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. In the study of Lou both groups receive standard treatment involving the administration of Lopinavir / Ritonavir or Darunavir / Cobicistat and Umifenovir, in combination with interferon α, in the Ivashchenko study standard treatment consisted of hydroxychloroquine or chloroquine in 15/20 (75.0%) of patients, lopinavir/ritonavir in 1/20 (5%). Four (20%) patients did not receive etiotropic treatment. In the Ivashchenko study, the concomitant therapy of COVID-19 in all groups included antibiotics, anticoagulants and/or immunosuppressants, as well as symptomatic treatment. in Dabbous 2020, the control group received hydroxychloroquine + oseltamivir which was considered as standard of care in Egypt. In Udwadia, standard treatment included antipyretics, cough suppressants, antibiotics, and vitamins [12]. In Ruzthentsova, standard care was according to the Russian Ministry of Health and the standards of the trial site, including umifenovir + intranasal interferon alpha-2b, or hydroxychloroquine, antipyretics, antibiotics, anticoagulants, vasoconstrictor drugs [11]. In Balykova 2020, SoC included hydroxychloroquine + azithromycin (n= 87); hydroxychloroquine (n = 8), lopinavir + ritonavir (n = 3), the combination with hydroxychloroquine, and azithromycin (n = 2).
b. In the Ivashchenko study we considered the group Favipiravir 1600/600mg
c. Downgraded by one level for risk of bias: some concerns regarding adequate randomization and deviation from intended intervention
d. Downgraded by two levels for imprecision: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
e. Downgraded by one level for risk of bias: some concerns regarding deviation form intended intervention and outcome measurement.
f. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
g. Downgraded by one level for risk of bias: some concerns regarding adequate randomization, deviation from intended intervention and selection of reported results
h. Downgraded by one level for risk of bias: some concerns regarding deviation form intended intervention, outcome measurement and selection of reported results
i. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for trivial benefit
j. Downgraded by one level for risk of bias: some concerns regarding adequate randomization, deviation from intended intervention, outcome assessment and selection of reported results
k. Outcome data from SNHTA
l. Downgraded by one level for risk of bias: some concerns regarding adequate randomization, deviation from intended intervention, outcome assessment

Table 4-2 Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir versus Umifenovir

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir
Comparison: Umifenovir
Both groups received additional therapies depending on the severity of the disease. For patients with moderate gravity: antibiotics, antivirals, glucocorticoids, Chinese complementary therapies, psychotropic substances, immunomodulators, nutritional support

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence	Comments
	Risk with Umifenovir	Risk with favipiravir					
All-cause mortality	-	-	Not estimable	Not estimable	236 (1)	very low[a,b,c]	No death occurred during the study period
Number of patients with any adverse events	233 per 1000	320 per 1000	RR 1.37 (0.90 to 2.08)	86 more per 1000 (from 23 fewer to 252 more)	236 (1)	low[d,e]	

Source: publication by Chen et al, 2020 [14], related to Chinese Clinical Trial Registry ID ChiCTR200030254 / ChiCTR200030254. Outcome data from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [23], GRADE assessment from covid-nma.com; descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded one levels for some concerns due to concerns during the randomization process and deviation from intended intervention
b. Downgraded two levels for imprecision: no events in both groups and low number of participants
c. Downgraded one level for indirectness: despite a multicenter design it's a single study from a single country, therefore results in this population might not be generalizable to other settings
d. Downgraded one level for some concerns due to concerns during the randomization process and deviation from intended intervention and outcome measurement
e. Downgraded one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
f. Not downgraded for indirectness: we presume that the adverse event rates, and the corresponding relative risks are similar across diverse settings

Table 4-3 Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir + interferon beta1b versus Hydroxychloroquine

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir + Interferon beta1b
Comparison: Hydroxychloroquine

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with Hydroxy-chloroquine	Risk with favipiravir + Interferon beta1b				
All cause mortality at day 14	133 per 1000	113 per 1000 (37 to 345)	RR 0.85 (0.28 to 2.59)	20 fewer per 1.000 (from 96 fewer to 212 more)	89 (1)	very low[a,b,c]
Number of patients discharged at day 14	689 per 1000	661 per 1000 (496 to 882)	RR 0.96 (0.72 to 1.28)	28 fewer per 1.000 (from 193 fewer to 193 more)	89 (1)	very low[b,c,d]
Admission to ICU[e]	178 per 1000	182 per 1000 (75 to 442)	RR 1.02 (0.42 to 2.48)	4 more per 1000 (from 103 fewer to 264 more)	89 (1)	very low[b,c,d,e]
Length of hospital stay (days) [e]	median (IQR): 7 (3-11)	median (IQR): 7 (4-12)	p value: 0.948	-	89 (1)	very low[c,d,e,f]

Source: publication by Khamis et al, 2020 [15]. Outcome data from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [24], GRADE assessment, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk; rob=risk of bias.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded by one level for rob: some concerns regarding randomization, deviation from intervention and selection of the reported results.
b. Downgraded one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
c. Downgraded one level for indirectness: it's a single study from a single country, results in this study population may not be generalizable to other settings
d. Downgraded by one level for rob: some concerns regarding randomization, deviation from intervention, outcome measurement and selection of the reported results.
e. outcome added by SNHTA, no other information available for this outcome
f. Downgraded one level for imprecision: low number of participants

Table 4-4 Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir versus Tocilizumab

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir
Comparison: Tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with Tocilizumab	Risk with favipiravir				
Number of patients with significant improvement in lung disease on CT	-	-	HR 3.16 (0.62 to 16.10) [a]		12 (1)	very low[b,c,d]
Number of patients with serious adverse events	No serious adverse event reported		-	-	12 (1)	very low[b,c,d]
Number of patients with any adverse event	400 per 1000	284 per 1000 (60 to 1000)	RR 0.71 (0.15 to 3.50)	116 fewer per 1.000 (from 340 fewer to 1.000 more)	12 (1)	very low[b,c,d]

Source: publication by Zhao et al, 2020 [16] related to Chinese clinical trial ChiCTR2000030894 and clinicaltrials.gov ID NCT04310228. Outcome data from the department of Epidemiology Lazio Regional Health Service (DEPLazio) in Italy [25], GRADE assessment, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. The study reports that there was a significant difference in favour of favipiravir (P = 0.034), which is not reflected by the HR.
b. Downgraded by one level for rob: some concerns regarding randomization, deviations from intervention, outcome measurement and selection of reported results
c. Downgraded by two levels for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
d. Downgraded by one level for indirectness: it's a single study from a single country, results in this study population may not be generalizable to other settings

Table 4-5 Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir + Tocilizumab versus Tocilizumab

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir + Tocilizumab
Comparison: Tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with Tocilizumab	Risk with Favipiravir + Tocilizumab				
Number of patients with significant improvement in lung disease on CT	-	-	HR 1.28 (0.39-4.23) [a]		21 (1)	very low[b,c,d]
Number of patients with serious adverse events	No serious adverse event reported		-	-	21 (1)	very low[b,c,d]
Number of patients with any adverse event	286 per 1000	643 per 1000 (186 to 1000)	RR 2.25 (0.65 to 7.73)	357 more per 1.000 (from 100 fewer to 1.000 more)	21 (1)	very low[b,c,d]

Source: publication by Zhao et al, 2020 [16] related to Chinese clinical trial ChiCTR2000030894 and clinicaltrials.gov ID NCT04310228. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [26], descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. The study reports that the cumulative rate of lung lesion remission on day 14 was not statistically significantly different in the combination group and the tocilizumab group (P = 0.575).
b. Downgraded by one level for rob: some concerns regarding randomization, deviations from intervention, outcome measurement and selection of reported results
c. Downgraded by two levels for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
d. Downgraded by one level for indirectness: it's a single study from a single country, results in this study population may not be generalizable to other settings

Table 4-6 Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir + Tocilizumab versus Favipiravir

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir + Tocilizumab
Comparison: Favipiravir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with Favipiravir	Risk with Favipiravir +Tocilizumab				
Number of patients with significant improvement in lung disease on CT	-	-	HR 2.66 (1.08-6.53) [a]		21 (1)	very low[b,c,d]
Number of patients with serious adverse events	No serious adverse event reported		-	-	21 (1)	very low[b,c,d]
Number of patients with any adverse event	286 per 1000	643 per 1000 (186 to 1000)	RR 2.25 (0.65 to 7.73)	357 more per 1.000 (from 100 fewer to 1.000 more)	21 (1)	very low[b,c,d]

Source: publication by Zhao et al, 2020 [16] related to Chinese clinical trial ChiCTR2000030894 and clinicaltrials.gov ID NCT04310228. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [27], descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. The study reports that the cumulative rate of lung lesion remission on day 14 was significantly higher in the combined group than in the favipiravir group (HR 2.66 95% CI [1.08-6.53], P = 0.019).
b. Downgraded by one level for rob: some concerns regarding randomization, deviations from intervention, outcome measurement and selection of reported results
c. Downgraded by two levels for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants
d. Downgraded by one level for indirectness: it's a single study from a single country, results in this study population may not be generalizable to other settings

Table 4-7 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Favipiravir versus Baloxavir

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir & standard care[a]
Comparison: Baloxavir & standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with Baloxavir + SOC	Risk with Favipiravir + SOC				
All-cause mortality	No death occurred		Not estimable	Not estimable	19 (1[a]) [10]	very low[b,c,d]
SARS-CoV-2 clearance up to 14 days	700 per 1000	630 per 1000 (371 to 1000)	RR 0.90 (0.53 to 1.54)	70 fewer per 1.000 (from 329 fewer to 378 more)	19 (1[a]) [10]	very low[d,e,f]
Number of patients with respiratory failure and respiratory distress syndrome	600 per 1000	810 per 1000 (336 to 1000)	RR 1.35 (0.56 to 3.28)	210 more per 1.000 (from 264 fewer to 1.000 more)	19 (1[a]) [10]	very low[d,f,g]

Source: publication by Lou et al, 2020 [10], related to Chinese Clinical Trial Registry ID: ChiCTR2000029544. GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio) [28]; outcome data, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk; SOC = standard of care.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Both groups receive standard treatment involving the administration of Lopinavir / Ritonavir or Darunavir / Cobicistat and Umifenovir, in combination with interferon α.
b. Downgraded by one level for rob: some concerns regarding randomization and deviations from intervention
c. Downgraded by two levels for imprecision: no events occurred in both groups and low number of participants
d. Downgraded by one level for indirectness: it's a single study from a single country, results in this study population may not be generalizable to other settings
e. Downgraded by one level for rob: some concerns regarding randomization, deviations from intervention and selection of the reported results
f. Downgraded by two levels for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of events or participants
g. Downgraded by one level for rob: some concerns regarding randomization, deviations from intervention and outcome measurement

Table 4-8 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of early Favipiravir versus late Favipiravir

Patient or population: Mild to moderate COVID-19 infection
Setting: Hospital inpatients
Intervention: early Favipiravir & standard care[a]
Comparison: late Favipiravir & standard care[a]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with Baloxavir + SOC	Risk with Favipiravir + SOC				
All-cause mortality up to day 28	No death occurred		Not estimable	Not estimable	88 (1[a]) [17, 18]	very low[b,c,d]
Time to hospital discharge			HR 1.96 (1.33 to 2.89)		88 (1[a]) [17, 18]	low[d,e]
2019-nCoV RT-PCR negativity						
Time to SARS-CoV-2 clearance up to 6 days			HR 1.42 (0.76 to 2.62)		88 (1[a]) [17, 18]	very low[d,f,g]
Time to SARS-CoV-2 clearance up to 10 days			HR 1.27 (0.74 to 2.1)		88 (1[a]) [17, 18]	very low[d,f,g]
50% reduction in SARS-Cov2 copy number			aOR 4.75 (0.88 to 25.76)		88 (1[a]) [17, 18]	very low[d,f,g]
Progression of COVID-19 disease:						
Transfer to ICU	No ICU transfers occurred		Not estimable	Not estimable	88 (1[a]) [17, 18]	very low[c,d,e]
Non invasive / mechanical ventilation	No events occurred		Not estimable	Not estimable	88 (1[a]) [17, 18]	very low[c,d,e]

Source: publication by Doi et al, 2020 [17, 18], related to the Japanese trial registry ID: JPRN-jRCTs041190120. This trial was excluded by the department of Epidemiology Lazio Regional Health Service (DEPLazio); GRADE assessment, outcome data, descriptions and layout by Swiss Network for health Technology Assessment (SNHTA), unless otherwise specified.
Abbreviations: CI: Confidence interval; RR=relative risk; SOC = standard of care; aHR=adjusted Hazard Ratio, adjusted for age and days between collection of the SARS-CoV-2-positive specimen and enrolment; aOR= adjusted Odds Ratio, adjusted for age and days between collection of the SARS-CoV-2-positive specimen and enrolment.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect
Very Low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Both groups receive standard treatment, which was not further described by the trial authors. Co-interventions reported and comparable across groups.
b. Downgraded by one level for rob: some concerns regarding randomization, deviation from intended intervention and selection of the reported results
c. Downgraded by two levels for imprecision: no events occurred in both groups and low number of participants
d. Downgraded by one level for indirectness: it's a single study from a single country, results in this study population may not be generalizable to other settings
e. Downgraded by one level for rob: some concerns regarding randomization, deviation from intended intervention, outcome measurement and selection of the reported results
f. Downgraded by two levels for rob: some concerns regarding randomization, selection of the reported results and high risk due to missing data
g. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm

Table 4-9 Study characteristics of included RCTs - Favipiravir versus standard of care

Author, year, reference number/Study name/Study ID	Lou et al, 2020 [10] Chinese Clinical Trial Registry ID: ChiCTR2000029544	Ivashchenko et al, 2020 [9] Clinicaltrials.gov ID NCT04434248	Dabbous et al, 2020 [8] Clinicaltrials.gov ID: NCT04349241 Trial acronym: FAV-001
Study design, study phase	Randomised open label, 3-arm controlled trial with parallel group assignment Blinding: none	Randomised open label, 3-arm controlled trial with parallel group assignment Phase 2/3 Blinding: none	Single center, two-arm, randomised open label controlled trial with parallel group assignment Phase 3 Blinding: none
Centres (single centre or multicentre), country, setting	Single center, China, hospital	Multicenter, Russia, hospital	Multicenter / Egypt, likely outpatients
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	N=30 (n1=10/ n2=10/ n3=10) Mean age : 53 21 males (70%) Severity : Mild: n=0 / Moderate: n=0/ Severe: n=0 Critical: n=0	N= 330, planned In interim report: 60 participants, n1=20/ n2=20/ n3=20** Mean age : 50.7 30 males (50%) Severity : Mild: n=0 / Moderate: n=60/ Severe: n=0 Critical: n=0	N=100 (n1=50 / n2= 50) Mean age : 36.4 50 males (50%) Severity : Mild: n=* / Moderate: n=*/ Severe: n=0 Critical: n=0 * all mild to moderate COVID-19, numbers not reported
Inclusion criteria	(1) Adults 18-85 years of age, either man or woman, who have signed the informed consent voluntarily; (2) Confirmed as COVID-19: positive results of throat swab or blood samples by real-time RT-PCR assay for 2019-nCoV; (3) No difficulty in swallowing oral drugs; (4) Ability to follow the protocol according to the judgment of researchers.	The eligible patients included hospitalized men and non-pregnant women of 18 years or older who signed the informed consent form, had moderate PCR-confirmed COVID-19 (positive test at screening), were able to administrate the drug orally and willing to use adequate contraception during the study and 3 months after its completion.	Adults between 18 and 80 years with confirmed COVID-19 documented by a diagnostic laboratory test (e.g., nasopharyngeal swab) at the time of illness and having mild to moderate symptoms according to the national protocol classification of patients.
Exclusion criteria	(1) Allergic constitution, known to be allergic to baloxavir marboxil or favipiravir or pharmaceutical excipients; (2) Weight < 40 kg; (3) Critical illness meeting one of the following conditions: respiratory failure and mechanical ventilation; shock; other organ failure requiring ICU monitoring and treatment; (4) Renal insufficiency (estimated creatinine clearance < 60 ml/min); (5) With any of the following laboratory parameter abnormalities detected within	1. Severe type of disease, with at least one of the following criteria: - Frequency of breath > 35 per minute, which does not decrease after the body temperature drops to normal or subfebrile values; - Blood oxygen saturation (SpO2) < 90% at rest; - Partial pressure of oxygen in arterial blood (PaO2) < 60 mm Hg; - Oxygenation index (RaO2/FiO2)â‰¤ 200 mm Hg;	Patients who had severe disease defined as presence of dyspnea, respiratory rate ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours or life-threatening disease defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure; Pregnant or lactating females or those participating in any investigational

Author, year, reference number/Study name/Study ID	Lou et al, 2020 [10] Chinese Clinical Trial Registry ID: ChiCTR2000029544	Ivashchenko et al, 2020 [9] Clinicaltrials.gov ID NCT04434248	Dabbous et al, 2020 [8] Clinicaltrials.gov ID: NCT04349241 Trial acronym: FAV-001
	24 hours before screening(according to local laboratory reference range): ALT or AST level > 5 times the upper limit of normal range (ULN) , or ALT or AST level > 3-fold ULN and total bilirubin level > 2-fold ULN; (6) Base on the researcher's judgment, there are other factors that may cause the subject to be forced to terminate the study midway, such as other serious diseases, serious laboratory examination abnormalities, other factors that affect the safety of the subject or study data and blood sample collection.	- Partial pressure of CO2 in arterial blood (PaCO2) < 60 mm Hg; - Septic shock. 2. Patients treated with lopinavir/ritonavir, ribavirin, arbidol, chloroquine, hydroxychloroquine, mefloquine, favipiravir within 7 days prior to screening. 3. Severe cardiovascular diseases currently or 6 months prior to randomization, including: New York Heart Association (NYHA) Class III or IV chronic heart failure, clinically significant ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation), unstable angina, myocardial infarction, heart and coronary vessel surgery, significant valvular heart disease, unconarterial hypertension with systolic blood pressure > 180 mm Hg and diastolic blood pressure > 110 mm Hg, pulmonary embolism or deep vein thrombosis. 4. Severe chronic renal impairment (GFR < 30 ml / min) or continuous renal replacement therapy, hemodialysis or peritoneal dialysis. 5. A history of cirrhosis or an increase in alanine aminotransferase (ALT) and / or aspartate aminotransferase (AST) > 5 times x upper limit of normal (ULN). 6. Severe diseases of the central nervous system, including seizures in history or conditions that may lead to their development; stroke or transient ischemic attack within 12 months prior to screening; head injuries or loss of consciousness within 12 months prior to screening; a brain tumor. 7. Significant uncontrolled concomitant disease, e.g. neurological, renal,	clinical study, other than observational, within the previous 30 days.

Author, year, reference number/Study name/Study ID	Lou et al, 2020 [10] Chinese Clinical Trial Registry ID: ChiCTR2000029544	Ivashchenko et al, 2020 [9] Clinicaltrials.gov ID NCT04434248	Dabbous et al, 2020 [8] Clinicaltrials.gov ID: NCT04349241 Trial acronym: FAV-001
		hepatic, endocrinological or gastrointestinal disorder which according to the Investigator, could prevent the patient from participating in the study 8. Malignancies that require chemotherapy within 6 months prior to screening. 9. Known HIV infection 10. Hypersensitivity to any component of the study drug. 11. Participation in other clinical studies or taking other study drugs within 28 days prior to screening. 12. Pregnant or lactating women or women planning to get pregnant during the clinical study; women of child-bearing potential (including non-sterilized by surgical means and during the post-menopause period less than 2 years) who do not use adequate contraception methods. 13. Inability to read or write, unwillingness to understand and follow procedures of study protocol, as well as any other concomitant medical or serious mental conditions that make the patient unfit to participate in the study, limit the legality of obtaining informed consent or can affect patient's ability to participate in the study.	
Intervention **(generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	N=10 Favipiravir (1600 or 2200mg initial 600mg mai) Co-Intervention: LPV/r or dar/cob+um Duration : Up to 14 days	N=20 Favipiravir 1800/800mg (1800mg day 1; 800mg days 2-14) Co-Intervention: Standard care Duration : 14 days	N=50 Favipiravir (1600/600 mg) Favipiravir, 1600 mg bid on day 1, 600 mg bid on day 2 to day 10 Co-Intervention: Standard care & anticoagulation, as described below Duration : 10 days
Comparator(s)	N=10 Control 1: Baloxavir marboxil (80mg)	Control 1: n=20	N=50 Standard care

Author, year, reference number/Study name/Study ID	**Lou et al, 2020 [10] Chinese Clinical Trial Registry ID: ChiCTR2000029544**	**Ivashchenko et al, 2020 [9] Clinicaltrials.gov ID NCT04434248**	**Dabbous et al, 2020 [8] Clinicaltrials.gov ID: NCT04349241 Trial acronym: FAV-001**
(standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Co-Intervention: LPV/r or dar/cob+um Duration : Days 1, 4 and 7 N=10 Control 2:Standard care (400mg/200mg) Co-Intervention: LPV/r or dar/cob+um	Favipiravir 1600/600mg (1600mg day 1; 600mg days 2-14) Co-Intervention: Standard care Duration : 14 days Control 2, n=20 Standard care based on approved clinical recommendations for treatment of COVID-19 in the Russian Federation (but not Favipiravir). Might include hydroxychloroquine, chloroquine, lopinavir/ritonavir or other recommended schemes.	Definition of Standard care: 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. All patients in both arms received anticoagulation in the form of enoxaparin 40mg SC for 14 days or 1mg/kg every 12 hours in case Ddimers>1000ng/ml for one month
Primary Outcome(s)	• Time to viral negativity by RT-PCR by day 13/14 • Time from randomization to clinical improvement, defined as the time from14 randomization to an improvement of two points (from the status at randomization) on a 15 seven-category ordinal scale or live discharge from the hospital, whichever came first.	• Elimination of SARS-CoV-2 by Day 10 (defined as two negative PCR tests with at least a 24-hour interval)	At timepoints 3, 7 and 14 days: • Achievement of two successive negative SARS-CoV-2 PCR analysis tests 48 hours apart by nasopharyngeal swab • normalization of body temperature for 48 hours • improvement of radiological abnormalities at day 14 • discharge rate out of the hospital
Patient-relevant secondary outcome(s)	• Percentage of subjects with viral negative by Day 7 • Incidence of mechanical ventilation by Day 14 • ICU admission by Day 14 • All-cause mortality by Day14	• Rate of viral clearance by Day 5 • Time to normalization of clinical symptoms (i.e. body temperature) • Changes on CT scan by Day 15 • incidence and severity of adverse events related to the study drug	None relevant to this report
Follow-up (days, months)	14 days	28 days	40 days (30 days post end of treatment)
Sponsor/ lead institution	The First Hospital Affiliated to Zhejiang University's Medical School	Chromis LLC	Sponsor: Ain Shams University

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

**Outcome data extracted from the trial registration site not included in the Summary of Findings Tables can be found in the Appendix Table 6-4

Table 4-10 Study characteristics of included RCTs – Favipiravir versus standard of care

Author, year, reference number/Study name/Study ID	Ruzhentsova 2020 [11] Clinicaltrials.gov ID: NCT04501783	Udwadia 2020 [12] Clinical Trials Registry-India ID: CTRI/2020/05/025114	Balykova 2020 [13] ** Clinicaltrials.gov ID: NCT04542694
Study design, study phase	Two-arm randomised open label controlled trial with parallel group assignment. Allocation: After stratification by the severity of their disease (mild or moderate), age (18-44 or ≥ 45 years) and CT severity subjects will be randomized at a rate of 2:1 to receive either TL-FVP-t + standard concomitant therapy or standard ethiptropic therapy (standard of care - SOC) Phase 3 Blinding: none	Two arm open label randomized controlled trial with parallel group assignment. Use of centralized randomization, randomization stratified by baseline disease severity. Phase 3 Blinding: none	Two-arm randomized open label controlled trial with parallel group assignment. Phase 3 Blinding: none
Centres (single centre or multicentre), country, setting	Multicenter, Russia, both hospital and outpatients	Multicenter, India, hospital	Multicenter, Russia, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	N=168 (n1=112 / n2= 56) Mean age : 41.8 79 males (70.5%) Severity : Mild: n=165 / Moderate: n=3/ Severe: n=0 Critical: n=0	N=150 (n1=75 / n2= 75) Mean age : 43.3 108 males (72%) Severity : Mild: n=89 / Moderate: n=58/ Severe: n=0 Critical: n=0	N=200 (n1=100 / n2= 100) Mean age : 49.7 97 males (48.5%) Severity : Mild: n=0 / Moderate: n=200/ Severe: n=0 Critical: n=0
Inclusion criteria	1) 18 – 60 years of age 2) had a diagnosis of mild to moderate COVID-19 without respiratory failure 3) with symptom manifestation no more than 6 days before the randomization 4) with SARS-CoV-2 confirmed by PCR of oro- or nasopharyngeal swabs and had received no previous etiotropic therapy for COVID-19	Age 18-75 years, infection with SARS-CoV-2 virus confirmed by RT-PCR within 48 hours prior to randomization, no participation in any other interventional clinical study, agreement to use effective contraception during the study and for ≥7 days following the last treatment, and, for female patients of child-bearing potential, a negative pre-treatment pregnancy test	Signing and dating of the Informed Consent Form of the Patient Information Leaflet (PIL) by patients. Men and women aged 18 to 80 years inclusive at the time of signing the Informed Consent Form in PIL. No difficulty with oral medication (e.g. swallowing disorder). Patient diagnosed with "Coronavirus infection caused by SARS-CoV-2 (confirmed)1, moderate severity form*" established in accordance with the Interim Guidelines of the Russian Ministry of Health for the prevention, diagnosis and treatment of a new coronavirus infection (COVID-19), (revision 6 of 28.04.2020). *Moderate severity form: fever above 38 °C, BR

Author, year, reference number/Study name/Study ID	Ruzhentsova 2020 [11] Clinicaltrials.gov ID: NCT04501783	Udwadia 2020 [12] Clinical Trials Registry-India ID: CTRI/2020/05/025114	Balykova 2020 [13] ** Clinicaltrials.gov ID: NCT04542694
			above 22/min, dyspnea during exercise, pneumonia (confirmed by lung CT), SpO2 < 95%, C reactive protein (CRP) serum level above 10 mg/l. Patient should be hospitalized no more than 48 hours before the start of the study therapy. Positive PCR result for presence of SARS-CoV-2 RNA at screening phase (results obtained within 7 days prior to screening are appropriate). Patient's consent to use reliable contraceptive methods throughout the study and within 1 month for women and 3 months for men after its completion.
Exclusion criteria	1) respiratory failure (SpO2 = 93 %) 2) the need for mechanical ventilation at screening 3) severe or extremely severe COVID-19 4) decreased level of consciousness or agitation 5) severe lung damage on computed tomography (CT) scans (subtotal diffuse ground glass induration of pulmonary tissue and pulmonary consolidation combined with reticular changes, the involvement of = 75 % of the lung parenchyma, hydrothorax (corresponding to = CT-4 stage according to Moscow Department of Health guidelines) 6) unstable hemodynamics 7) any of the following abnormal laboratory tests at screening: AST or ALT level > 2·5 x upper limit of normal (ULN), platelet count < 50.109/L 8) moderate or severe chronic obstructive pulmonary disease or asthma, severe chronic cardiovascular	Severe infection (defined as need for invasive or non-invasive ventilator support, extracorporeal membrane oxygenation [ECMO] or shock requiring vasopressor support), oxygen saturation ≤93% or arterial oxygen partial pressure or fraction of inspired oxygen of ≤300 mmHg, requiring ICU care for management of ongoing clinical status, inability to take or tolerate oral medications, allergy or hypersensitivity to favipiravir, asthma or chronic obstructive lung disease, severe liver disease (underlying liver cirrhosis or alanine aminotransferase/aspartate aminotransferase elevated over 5 times the upper limit of normal [ULN]), history of gout or hyperuricemia (above the ULN), prolonged QT (defined as QTcF ≥450 msec for men and as QTcF ≥470 msec for women), severely reduced left ventricular function (ejection fraction <30%), or severe renal impairment (creatinine clearance <30 mL/min), or having received continuous renal	Hypersensitivity to favipiravir and/or other components of the study drug. Impossibility of CT procedure (for example, gypsum dressing or metal structures in the field of imaging). The need to use drugs from the list of prohibited therapy. Need for treatment in the intensive care unit. Impaired liver function (AST and/or ALT ≥ 2 UNL and/or total bilirubin ≥ 1.5 UNL) at the time of screening. Impaired kidney function (creatinine clearance according to Cockcroft-Gault formula less than 45 ml/min) at the time of screening. Positive testing for HIV, syphilis, hepatitis B and/or C. Chronic heart failure FC III-IV according to New York Heart Association (NYHA) functional classification. Malabsorption syndrome or other clinically significant gastrointestinal disease that may affect absorption of the study drug (non-correctable

Author, year, reference number/Study name/Study ID	Ruzhentsova 2020 [11] Clinicaltrials.gov ID: NCT04501783	Udwadia 2020 [12] Clinical Trials Registry-India ID: CTRI/2020/05/025114	Balykova 2020 [13] ** Clinicaltrials.gov ID: NCT04542694
	disorders, severe obesity, diabetes mellitus, chronic renal failure, chronic moderate or severe hepatic disorders, imparted immune response (HIV, cancer, autoimmune diseases, immunosuppressive therapy)	replacement therapy, hemodialysis or peritoneal dialysis	vomiting, diarrhea, ulcerative colitis, and others). Malignancies in the past medical history. Alcohol, pharmacological and/or drug addiction in the past medical history and/or at the time of screening. Schizophrenia, schizoaffective disorder, bipolar disorder, or other history of mental pathology or suspicion of their presence at the time of screening. Severe, decompensated or unstable somatic diseases (any disease or condition that threaten the patient's life or impair the patient's prognosis, and also make it impossible for him/her to participate in the clinical study). Any history data that the investigating physician believes could lead to complication in the interpretation of the study results or create an additional risk to the patient as a result of his/her participation in the study. Patient's unwillingness or inability to comply with procedures of the Study Protocol (in the opinion of physician investigator). Pregnant or nursing women or women planning pregnancy. Participation in another clinical study for 3 months prior to inclusion in the study. Other conditions that, according to the physician investigator, prevent the patient from being included in the study.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Favipiravir (1800/800 mg): 1800 mg BID on day 1, followed by 800 mg on day 2 to 10 (maximum) Co-Intervention: Standard care Duration : 10 days	Favipiravir (1800/800 mg): use of 200 mg tablets for oral use. 3,600 mg (1,800 mg BID) on day 1 + 1,600 mg (800 mg BID) on day 2 to 14 days (maximum). Co-Intervention: Standard care Duration : 14 days	Favipiravir (1600/600mg; Areplivir): 1600 mg (8 tablets) on day 1, BID; 600 mg (3 tablets) BID on day 2-14. Duration : 14 days
Comparator(s)	Standard care	Standard care	Standard care

Author, year, reference number/Study name/Study ID	Ruzhentsova 2020 [11] Clinicaltrials.gov ID: NCT04501783	Udwadia 2020 [12] Clinical Trials Registry-India ID: CTRI/2020/05/025114	Balykova 2020 [13] ** Clinicaltrials.gov ID: NCT04542694
(standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Definition of Standard care: All patients received supportive care according to the guideline of the Russian Ministry of Health (MoH) and the standards of the trial site, including umifenovir + intranasal interferon alpha-2b, or hydroxychloroquine, antipyretics, antibiotics, anticoagulants, vasoconstrictor drugs, etc. Duration : 10 days	Definition of Standard care: antipyretics, cough suppressants, antibiotics, and vitamins. Drugs thought to have antiviral activity against SARS CoV- 2 (including hydroxychloroquine) were prohibited. Prohibited concomitant medications included hydroxychloroquine or chloroquine, pyrazinamide, repaglinide, theophylline, and famciclovir or sulindac. Duration : 14 days	Definition of Standard care: standard therapy prescribed in accordance with the recommended treatment regimens included in the Interim Guidelines for the prevention, diagnosis and treatment of new coronavirus infection (COVID-19) approved by the Russian Ministry of Health (but not Favipiravir) by decision of the investigator and taking into account the availability of drugs at the study site. SoC included hydroxychloroquine + azithromycin (n= 87); hydroxychloroquine (n = 8), lopinavir + ritonavir (n = 3), the combination with hydroxychloroquine, and azithromycin (n = 2). Duration : 14 days
Primary Outcome(s)	• Time to clinical improvement • time to viral clearance Both during the time from randomization to Day 28.	• Time from randomization to cessation of oral shedding of the SARS-CoV-2 virus (28-days maximum; specified as a negative RT-PCR result for both oropharyngeal and nasopharyngeal swabs)	• Time to clinical improvement at 10 days– a decrease by 1 category in the assessment on the Categorical scale of clinical improvement of the World Health Organization • the number of patients who achieved clinical improvement by 2 categories at day 10
Patient-relevant secondary outcome(s)	• rate of clinical improvement at Day 7 • the rate of viral clearance at Day 5 • rate of clinical improvement at Day 14 • the rate of viral clearance at separate days (3, 7, 10, 14, 21, and 28) • the time to body temperature normalization (defined as body temperature < 37°C without antipyretics for at least 48 hours), • the rate of resolution of lung changes on CT at Day 14	• time to clinical cure for patients who presented with clinical signs and symptoms at baseline.* • time to first use of high flow supplemental oxygen, ventilation (non-invasive or mechanical), or ECMO • time to hospital discharge. Hospital discharge was dependent on achieving both RT-PCR negativity on 2 consecutive tests and maintaining clinical cure for ≥72 hours • Rates of clinical cure and SARS-CoV-2 RT-PCR negativity at Days 4, 7, 10, and 14	• time to achieve elimination of the virus and CT scan of the lungs. The elimination of the virus was considered achieved in the absence of the RNA of the SARS-CoV-2 virus, according to the results of the study by the PCR method, in 2 swabs from the oropharynx, taken at an interval of at least 24 hours • new coronavirus infection Safety outcomes • frequency and severity of adverse events (AEs) and serious AEs (SAEs)

Author, year, reference number/Study name/Study ID	Ruzhentsova 2020 [11] Clinicaltrials.gov ID: NCT04501783	Udwadia 2020 [12] Clinical Trials Registry-India ID: CTRI/2020/05/025114	Balykova 2020 [13] ** Clinicaltrials.gov ID: NCT04542694
	• average score according to WHO 8-Category Ordinal Scale at Days 7 and 14 • the time to resolution of the main disease symptoms • the rate of hospitalization for outpatients • the rate of artificial lung ventilation (ALV) use • the rate of transfer to intensive care unit (ICU) and the death rate during the 28 days Safety outcomes: • the rate and severity of AEs and serious AEs (SAE) • rate of grade 3 and 4 AEs • rate of study discontinuation due to AE/SAE	• frequency of serious adverse events (SAEs) • treatment emergent adverse events (TEAEs)	• frequency of any AEs that led to the withdrawal of the studied drugs • the frequency of significant changes in vital signs
Follow-up (days, months)	28 days	28 days	30 days
Sponsor/ lead institution	Sponsor: R-Pharm	Glenmark Pharmaceuticals Ltd, India	Promomed, LLC

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

**Outcome data extracted from the trial registration site not included in the Summary of Findings Tables can be found in the Appendix Table 6-4

ł Clinical cure in Udwadia 2020 was based on clinician assessment and defined as recovery of fever (axillary temperature ≤97.8°F), respiratory rate of ≤20 breaths/minute, oxygen saturation ≥98% without oxygen supplementation (which was later revised to align with the discharge criterion of ≥95% oxygen saturation issued by the Indian Ministry of Health prior to the start of the study), and cough relief (mild or no cough) maintained for ≥72 hours.

Table 4-11 Study characteristics of included RCTs – Favipiravir versus Umifenovir

Author, year, reference number/Study name/Study ID	**Chen et al, 2020 [14]** **Chinese Clinical Trial Registry ID ChiCTR200030254 / ChiCTR200030254**
Study design, study phase	Randomised, open label, controlled trial with parallel group assignment Blinding: Unblinded
Centres (single centre or multicentre), country, setting	Multicenter, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	240 participants (n1=120 / n2= 120) Mean age: not reported 110 males (45.8%) Severity : Mild: n=0 / Moderate: n=209/ Severe: n=24 Critical: n=3
Inclusion criteria	Patients were assessed for eligibility on the basis of: (1) aged 18 years or older; (2) voluntarily provided informed consent; (3) initial symptoms were within 12 days; (4) Diagnosed as COVID-19 pneumonia. According to the Chinese Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia at that moment,10,11 COVID-19 could be diagnosed without a positive SARS-CoV-2 nucleic acid test result by: (1) a positive chest CT scan; (2) significant clinical manifestation including pyrexia, cough, breath difficulty and other indications of viral infection of lower respiratory tract; and (3) laboratory results indicating lymphopenia and (optional) leukopenia. Hence, male and female adult patients with clinically confirmed COVID-19 including moderate, severe or critical types of COVID-19 were eligible.
Exclusion criteria	Patients were excluded if they meet any of following criteria: (1) allergic to Favipiravir or Arbidol; (2) with elevated ALT/AST (>6x upper limit of normal range) or with chronic liver disease (cirrhosis at grade Child-Pugh C); (3) Severe/Critical patients whose expected survival time were <48 hours; (4) female in pregnancy; (5) HIV infection; or (6) considered unsuitable by researchers for the patient's best interest.
Intervention **(generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	N=120 Favipiravir (1600mg initial 600mg maintenance) Co-Intervention: not described Duration : 7 days
Comparator(s) **(standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	N=120 Arbidol, Umifenovir (200mg) not further described Duration : 7 days
Primary Outcome(s)	• Clinical recovery rate at 7 days or end of treatment
Patient-relevant secondary outcome(s)	• All-cause mortality during the trial • The rate of respiratory failure during the trial • The rate of auxiliary oxygen therapy or noninvasive mechanical ventilation during the trial • After one week of treatment, the negative rate of 2019-nCOV RT PCR test for upper respiratory tract specimens • The rate of ICU admission during the trial • The time from randomization to fever reduction • The time from randomization to cough relief

Author, year, reference number/Study name/Study ID	**Chen et al, 2020 [14]** **Chinese Clinical Trial Registry ID ChiCTR200030254 / ChiCTR200030254**
	• The time from randomization to dyspnea relief • Incidence of serious adverse events (SAE) during the trial
Follow-up (days, months)	7 days
Sponsor/ lead institution	Zhongnan Hospital of Wuhan University

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Source: https://covid-nma.com/living_data/index.php, published reports and trial registrations.

Table 4-12 Study characteristics of included RCTs - Favipiravir + Interferon beta1b versus Hydroxychloroquine

Author, year, reference number/Study name/Study ID	**Khamis et al, 2020 [15]**
Study design, study phase	2-arm randomized open label controlled trial with parallel group assignment Blinding: none
Centres (single centre or multicentre), country, setting	Single center / Oman, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Interim analyses: N=89 (n1=44 / n2= 45) Mean age : 55 52 males Severity: moderate to severe, numbers not reported
Inclusion criteria	Age between 18-75 years, confirmed SARS-CoV-2 infection by RT-PCR test on respiratory tract specimens, moderate to severe COVID-19 pneumonia according to the WHO interim guidelines case definitions (WHO/2019 nCoV/ Surveillance Case Definition /2020.1), the interval between symptoms onset and randomization is no >10 days; for female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pretreatment serum or urine pregnancy test, eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment; not participating in any other interventional drug clinical study before completion of the present one.
Exclusion criteria	Age above 75, refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of favipiravir; severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the upper limit normal ; gout or history of gout or hyperuricemia; known severe renal impairment with creatinine clearance (CrCl) of <30 mL/min or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis , known allergy or hypersensitivity to favipiravir or pregnant or lactating women.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Favipiravir+Interferon beta-1b: Favipiravir 1600 mg on day 1; 600 mg bid on day 2 to 10 (maximum) plus interferon Beta-1b at a dose of 8 million IU bid for 5 days through a vibrating mesh aerogen nebulizer (Aerogen Solo) Co-Intervention: Standard care Duration : 10 days; 5 days

Author, year, reference number/Study name/Study ID	**Khamis et al, 2020 [15]**
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Hydroxychloroquine (400/200 mg): SoC: based on the national guidelines that had HCQ 400 mg bid on day 1, 200 mg BID on day 2 to 7 Duration : 7 days
Primary Outcome(s)	time from assignment to clinical recovery, the normalization of inflammatory markers and improvement in oxygen saturation that is maintained for at least 72 hours.
Patient-relevant secondary outcome(s)	• All-cause mortality • Number of patients discharged at day 15 • Admission to ICU • Length of hospital stay
Follow-up (days, months)	14 days
Sponsor/ lead institution	Royal Hospital, Muscat, Oman

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-13 Study characteristics of included RCTs – Favipiravir +/- Tocilizumab

Author, year, reference number/Study name/Study ID	**Zhao et al, 2020 [16]** **Chinese clinical trial ID ChiCTR2000030894** **Clinicaltrials.gov ID NCT04310228**
Study design, study phase	Three-arm open label randomized controlled trial with parallel group assignment Phase not described Blinding: none
Centres (single centre or multicentre), country, setting	Multicenter, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	N=26 (n1=7/ n2=14/ n3=5) Mean age : NR 14 males Severity : Mild: n=0 / Moderate: n=12/ Severe: n=13 Critical: n=1
Inclusion criteria	Laboratory-confirmed cases according to Chinese guidelines of COVID-19; Male or female more than 18 years old; Increased interleukin-6; Sign the informed consent
Exclusion criteria	Allergic to favipiravir or tocilizumab;Pregnant or lactating woman; ALT or AST >5 times of upper limit of normal; Patients with active hepatitis, tuberculosis, and definite bacterial or fungal infections; Other conditions judged by the investigators
Intervention **(generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	N1=7 Favipiravir (1600/600 mg): 1600 mg BID on day 1; 600mg BID on day 2-7 (maximum). Oral administration. Co-Intervention: Standard care Duration : 7 days N2=14 Favipiravir + Tocilizumab group: Favipiravir: 1600 mg BID on day 1, 600 mg BID on day 2-7 (maximum). Oral administration. Tocilizumab: The first dose is 4 ~ 8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg Co-Intervention: Standard care Duration : Favipiravir 7 days, Tocilizumab 1 day N3=5 Tocilizumab (400 mg), as described above Co-Intervention: Standard care Duration : 1 day
Comparator(s) **(standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	See above
Primary Outcome(s)	• cumulative lung lesion remission rate (lung CT examination indicated absorption of lung inflammation)

Author, year, reference number/Study name/Study ID	**Zhao et al, 2020 [16]** **Chinese clinical trial ID ChiCTR2000030894** **Clinicaltrials.gov ID NCT04310228**
	• But at trial register: clinical cure rate at 3 months. Definition of clinical cure: the viral load of the respiratory specimen was negative for two consecutive times (the interval between the two tests was greater than or equal to one day), the lung image improv
Patient-relevant secondary outcome(s)	• improvement of clinical symptoms (cough, diarrhea, dyspnea, fever, myalgia) before and after treatment Safety outcomes • frequencies of adverse events
Follow-up (days, months)	60 days
Sponsor/ lead institution	Peking University First Hospital

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Source: https://covid-nma.com/living_data/index.php, published reports and trial registrations.

Table 4-14 Study characteristics of included RCTs – Early favipiravir versus late favipiravir

Author, year, reference number/Study name/Study ID	Doi 2020 [17] Japan Register of Clinical Trials: jRCTs041190120
Study design, study phase	Two-arm randomized open label controlled trial with parallel group assignment Phase 2 Blinding: open
Centres (single centre or multicentre), country, setting	Multicenter, Japan, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	N=89 (n1=44 / n2= 45) Mean age : NR 46 males Severity: asymptomatic and mildly ill, numbers not reported. Mild: n=* / Moderate: n=0 Severe: n=0 Critical: n=0
Inclusion criteria	• age 16 or older, • inpatient, • positive RT-PCR test for SARS-CoV-2 from a pharyngeal or nasopharyngeal swab specimen collected within 14 days, • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, • able to remain hospitalized for 6 days or longer, • negative pregnancy test (pre-menopausal female only), • (7) written consent for participation
Exclusion criteria	• performance status of 2 or greater, • severe hepatic disease, • need for dialysis, • altered mental status,

Author, year, reference number/Study name/Study ID	Doi 2020 [17] Japan Register of Clinical Trials: jRCTs041190120
	• pregnancy, • female patients who do not agree to use effective contraceptive methods, • male patients with female partners who do not agree to the use of effective contraceptive methods, • hereditary xanthinuria, • hypouricemia or history of xanthine urolithiasis, • uncontrolled gout or hyperuricemia, • immunosuppressive conditions, • receipt of systemic antiviral agent against SARS-CoV-2 within 28 days
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	N=44 Early Favipiravir (800 mg): immediate favipiravir (Avigan Tablets 200mg) administered orally between Day 1 and Day 10, 1800 mg tid on Day 1 followed by 800 mg tid from Day 2 Co-Intervention: Standard care Duration : 6-10 days
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	N=44 Late Favipiravir (800 mg): delayed favipiravir (Avigan Tablets 200mg) administered orally between Day 6 and Day 15, 1800 mg tid on Day 6 followed by 800 mg tid from Day 7 Co-Intervention: Standard care Duration : 6-10 days
Primary Outcome(s)	In published report • Time to SARS-CoV-2 clearance and presence or absence of SARS-CoV-2 clearance by RT-PCR of nasopharyngeal specimens by day 6 At trial registration: • Proportion of subjects with clearance of SARS-CoV2 in nasopharyngeal swab on Day 6 • Proportion of subjects with 90% reduction in SARS-CoV2 copy number in nasopharyngeal swab between Day 1 and Day 6 • Change of SARS-CoV2 copy number in nasopharyngeal swab
Patient-relevant secondary outcome(s)	•
Follow-up (days, months)	28 days
Sponsor/ lead institution	Fujita Medical University Hospital

Table 4-15 Summary of safety from observational studies (AE and SAE) of Favipiravir

Author, year	Cai 2020 [16]	Calik 2020 [20]
Country	China	Turkey
Sponsor / lead institution	The Third People's Hospital of Shenzhen	Not described
Intervention/Product (drug name)	Favipiravir (FV) by Zhejiang Hisun Pharmaceutical Co., LTD) & interferon-alpha	Favipiravir containing regimens FV (not described)
Dosage	Favipiravir 1600 mg po b.i.d. on day 1 and 600 mg po b.i.d. on days 2–14 plus interferon-α (60 μg b.i.d.) by aerosol inhalation	FV: not reported
Comparator	Lopinavir/ritonavir, 200 mg/50 mg) 500 mg po b.i.d. on days 1–14 plus interferon-α 60 μg b.i.d. by aerosol inhalation	hydroxychloroquine (HQ) only, dose not reported HQ plus azithromycin (AZ), dose not reported
Study design	Chinese Clinical Trial Registry: ChiCTR2000029600 Open-label, nonrandomized, before-after controlled study with ambispective datacollection (prospective consecutive inclusion of laboratory confirmed Covid-19 patients received the experimental interventions from 30-01-2020 to 14-02-2020; retrospective inclusion of patient who had initially been treated with control intervention from 24-01-2020 to 30-01-2020.)	Prospective observational single center study
Setting	Hospital	Hospitalised
Number of pts	Overall: 80 Experimental: 35 Control: 45	174 168 described FV: 32 HQ: 23 HQ-AZ: 113
Inclusion criteria	• aged 16–75 years old • nasopharyngeal swabs samples tested positive for the novel coronavirus RNA • duration from disease onset to enrolment was less than 7 d • willing to take contraception during the study and within 7 d after treatment • no difficulty in swallowing the pills • Key exclusion criteria • severe clinical condition (detailed defition provided in publication [16]) • chronic liver and kidney disease and reaching end stage; • previous history of allergic reactions to FPV or LPV/RTV • pregnant or lactating women; women of a childbearing age with a positive pregnancy test, breastfeeding, miscarriage, or within 2 weeks after delivery • participated in another clinical trial against SARSCoV-2 treatment currently or in the past 28 d.	• probable/confirmed adult COVID-19 patients hospitalized in a tertiary care hospital COVID-19 wards between March 20- April 30, 2020

Author, year	Cai 2020 [16]	Calik 2020 [20]
Exclusion criteria	• severe clinical condition (meeting one of the following criteria: a resting respiratory rate greater than 30 per minute, oxygen saturation below 93%, oxygenation index (OI) < 300 mmHg, respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment); • chronic liver and kidney disease and reaching end stage; • previous history of allergic reactions to FPV or LPV/RTV • pregnant or lactating women • women of a childbearing age with a positive pregnancy test • breastfeeding • miscarriage, or within 2 weeks after delivery • participated in another clinical trial against SARSCoV-2 treatment currently or in the past 28 d.	• Critically-ill patients with sepsis and/or acute respiratory distress syndrome (ARDS) requiring intensive care unit (ICU) care at the time of admission
Age of patients (yrs)	47.0 (35.8–61.0)†	45.5 (median)
Disease severity	Nonsevere COVID-19	Mild to Severe
Follow-up (months)	Up to 14 days	Not described, median hospitalisation 4 days (0 to 28 days)
Loss to follow-up, n (%)	0 (0%)	Not described
RoB	High RoB Very low-quality evidence	High RoB Very low-quality evidence
Safety - Outcomes		
Overall AEs, n (%)	FV: 4 / 35 (11.43%) L/R: 25 / 45 (55.56%)	-
Serious AE (SAE), n (%)	-	-
Most frequent AEs n (%)	Diarrhea FV: 2 (5.7%) L/R: 5 (11.1%) Vomiting FV: 0 (0.0%) L/R: 5 (11.1%) Nausea FV:0 (0.0%) L/R: 6 (13.3%) Rash FV: (0 0.0%) L/R: 4 (8.9%) Liver and kidney injury FV: 1 (2.9%) L/R: 3 (6.7%)	Transaminases > 100 U/L FV: 10 (35.7%) HQ: 1 (4.5%) HQ-AZ 3 (2.9%) Nausea & vomiting FV: 5 (17.9%) HQ: 1 (4.3%) HQ-AZ: 5 (4.7%)
Most frequent SAEs, n (%)	-	-
AEs of special interest, n (%)	-	-
Death as SAE, n (%)	-	-

Author, year	Cai 2020 [16]	Calik 2020 [20]
Withdrawals due AEs, n (%)	FV: (0%) L/R: (0.0%))	FV: 0 (0%) HQ: 0 (0%) HQ-AZ: 0 (0%)

*** by arms, if available, (Robins-I): https://training.cochrane.org/handbook/current/chapter-25; ǂ** unclear whether to be counted as "death as SAE", the patient had disseminated intravascular coagulation on admission that gradually progressed to multiple organ failure durng the study.
Abbreviations: FV = favipiravir; HQ = hydroxychloroquine AZ = azithromycin; L/R = Lopinavir/ritonavir

Table 4-16 Summary of safety from observational studies (AE and SAE) of Favipiravir

Author, year	Doi 2020 [21]
Country	Japan
Sponsor / lead institution	Not described, likely Fujita Health University
Intervention/Product (drug name)	Favipiravir (Avigan) & Concomitant use of: Ciclesonide, an inhaled steroid agent in 41.6% Lopiniavir-ritonavir in 3.4% Other therapy related to COVID-19 – not further defined: 27.7%
Dosage	Favipiravir: • 1,800 mg orally bid on day 1; 800 mg orally bid on subsequent days in 92.8% of the patients. • 1,600 mg orally bid on day 1; 600 mg orally bid on subsequent days in 5.4% of the patients Median duration of 11 days (mean 10.4; SD 5.6).
Comparator	none
Study design	Prospective single arm study: real time registry in 407 participating centers with limited data cleaning
Setting	Hospitalised
Number of pts	2158
Inclusion criteria	• confirmed COVID-19 patients admitted to one of the 407 participating hospitals from February to May 2020 • negative pregnancy test, agreeing to an effective contraception during and 10 days after administration of favipiravir
Exclusion criteria	• none reported
Age of patients (yrs)	Mean not reported. 52.3% were aged 60 years or older
Disease severity	• Mild disease not requiring supplemental oxygen n=976 (45.2%) • Moderate disease requiring supplemental oxygen: n=947 (43.9%) • Severe disease requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO): n=239 (10.9%)
Follow-up (months)	Up to 14 days after starting favipiravir intake
Loss to follow-up, n (%)	patient demographics, clinical status at day 7, clinical status at day 14, clinical outcome at one month were available for 2,127, 1,713, 1,282 and 1,918 cases
RoB	Robins-I is not applicable to uncontrolled study designs, no generally accepted risk of bias tool exists for uncontrolled studies. Limitations reported by authors: "this study utilizes a survey function in an effort to prioritize timeliness of the data and ease of data entry at each hospital, and only limited data cleaning has been performed. Also, since information on patient transfer is not collected, the same patients may be registered more than once if they received favipiravir at multiple hospitals" As the authors omitted the desciption of the sampling method of the patients, the completeness of the database and the attribution methods of adverse events, the risk of bias may be described as unclear.
Overall AEs, n (%)	Adverse events possibly or likely related to favipiravir use: 532/2158 (24.65%)
Serious AE (SAE), n (%)	-

Author, year	Doi 2020 [21]
Most frequent AEs n (%)	Hyperuricemia: 335 (15.52%) liver injury or liver function test abnormalities: 159 (7.37%)
Most frequent SAEs, n (%)	-
AEs of special interest, n (%)	-
Death as SAE, n (%)	-
Withdrawals due AEs, n (%)	-

*** by arms, if available, (Robins-I): https://training.cochrane.org/handbook/current/chapter-25;**

Abbreviations: FV = favipiravir; HQ = hydroxychloroquine AZ = azithromycin; L/R = Lopinavir/ritonavir; BID = twice daily

Table 4-17 Ongoing phase 3 trials of single agents: Favipiravir

Trial Identifier/registry ID(s)/contact	EudraCT ID: 2020-001449-38; Clinicaltrials.gov: NCT04373733 Trial acronym: PIONEER Contact: Pallav Shah / Bobby Mann; research.development@chewest.nhs.uk	EUdraCT ID: 2020-001115-25 ClinicalTrials.gov ID: NCT04336904 Other trial ID: HS216C17 Contact: Giuliano Rizzardini	ClinicalTrials.gov ID: NCT04425460 EudraCT ID: 2020-001608-40 Other Study ID: HS216C17(MRCT) Contact: Dionisio Barattini; barattini@operacro.ro
Study design, study phase	Phase 3 Two-center two-arm randomised open label controlled trial with parallel group design*	Phase 3 Single center two-arm randomised double blind control trial with parallel group design	Phase 3 Multicenter two-arm randomised double blind trial with parallel group design
Recruitment status	Recruiting (last update posted at trial registry at 7 July 2020)	Active, not recruiting (last update posted at trial registry at 8 April 2020)	Not yet recruiting (last update posted at trial registry at 11 June 2020)
Number of Patients, Disease severity**	450 Not described, referred to hospital for period expected to last at least 1 day*	100 Moderate Covid-19	256 Moderate Covid-19
Setting (hospital, ambulatory,..)	Hospitalized patients	Outpatient and hospitalised patients	Outpatient and hospitalised patients
Intervention (generic drug name and dosage)	Avigan, 1800 mg bid on day 1, 800 mg twice per day on day 2 to 10*, oral or nasogastric intake	Favipiravir, 1800 mg bid on day 1, 600 mg tid on day 2 to 14, route of administration not described & standard care	Favipiravir, 1800 mg bid on day 1, 600 mg tid on day 2 to 14, route of administration not described, & standard care according to national / local guidelines
Comparator (standard care or generic drug name and dosage)	UK standard of care*	Placebo, given with the same dose shedule as Avigan & standard care	Placebo, given with the same dose shedule as the active intervention & standard care according to national / local guidelines
Primary Outcome(s)	• Time to clinical improvement (post randomisation) by two points on a seven-category ordinal scale# or live discharge from the hospital, whichever comes first. Time point: until discharge from inpatient care, 28 day from enrolment or death k	Time from randomization to clinical recovery, up to 90 days	Time from randomization to clinical recovery, up to 28 days
Sponsor/ lead institution, country (also country of recruitment if different)	Sponsor: Chelsea and Westminster Hospital NHS Foundation Trust, UK	Sponsor: ASST Fatebenefratelli Sacco, Italy	Sponsor: Zhejiang Hisun Pharmaceutical Co. Ltd., Recruitment sites in China (n=2), Germany (n=2); Romania (n=4)

*as described at clinicaltrials.gov; **Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19; # = The seven-category ordinal scale:
1: Not hospitalised with resumption of normal activities 2: Not hospitalised, but unable to resume normal
3: Hospitalised, not requiring supplemental oxygen
4: Hospitalised, requiring supplemental oxygen
5: Hospitalised, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation or both
6: Hospitalised, requiring ECMO (Extra-corporal membrane oxygenation), invasive mechanical ventilation or both
7: Death
Abbreviations: see "List of abbreviations" at page 5.

Table 4-18 Ongoing phase 3 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrial.gov: NCT04411433 Contact: Prof. Ateş Kara; +90 532 4135130; ateskara@hacettepe.edu.tr	ClinicalTrial.gov: NCT04319900 ChiCTR2000030987 Other trial ID: 2020-K-24-2 Contact: Shumin Wang; +86 13488760399; shuminwang7000@163.com	Iranean registry of Randomised Trials (IRCT) ID: IRCT20151227025726N14 Contact: Farzaneh Dastan; +98 21 8820 0118; f_dastan@sbmu.ac.ir
Study design, study phase	Phase 3 Multicenter, six-arm randomised open label controlled trial with parallel group assignment. Randomisation in 2:1:2:2:2:1 ratio	Phase 3 Multicenter three-arm randomised double blind controlled trial with parallel group assignment	Phase 3 Single center, 2-arm randomised open label controlled trial with parallel group assignment. Block randomization, with block size of four.
Recruitment status	Active, not recruiting (last update posted 1 Feb. 2021)	Recruiting (last update posted 24 March 2020)	Unknown (last update at registry on 4th of July 2020)
Number of Patients, Disease severity*	1008 (actual) Mild to moderate Covid-19	150 Non-severe Covid-19	84 Moderate COVID-19 (adults with COVID-19 by RT-PCR test, with oxygen saturation less than 93%, fever more than 72 hours before admission, and bilateral pulmonary infiltration. Mild and critical phase of COVID-19 are excluded
Setting (hospital, ambulatory,..)	Hospital	Not described	Hospitalised
Intervention (generic drug name and dosage)	Trial arm 1: • Favipiravir, 1600 mg bid on day 1, 600 mg bid on day 2 to 5. Trial arm 2: • Favipiravir, 1800 bid on day 1, 800 mg bid on day 2 to day 5 mg Trial arm 3: • Favipiravir, 1600 bid on day 1, 600 mg bid on day 2 to day 5 combined with Hydroxychloroquine 400 mg bid on day 1, 200 mg bid on day 2 to day 5 Trial arm 4: • Favipiravir, 1600 mg bid on day 1, 600 mg bid on day 2 to 5 combined with Azithromycin, 500 mg on day 1, 250 mg on day 2 to day 5 Trial arm 5: • Hydroxychloroquine, 400 mg bid on day 1, 200 mg bid for on day 2 to 5	Single agent trial arm: • favipiravir 1600 mg bid on day 1, 600 mg bid on day 2 to day 10, oral intake Combined agent trial arm: • favipiravir 1600 mg bid on day 1, 600 mg bid on day 2 to day 10, oral intake & chloroquine phosphate 500 mg bid on day 1, 500 mg once daily on day 2 and day 3, 250 mg once daily on day 4 to day 10, oral intake	Favipiravir arm: • Favipiravir (Toliddaru-Sobhan Oncology company, Iran) at dose of 1600 mg BID for one day and then 600 mg BID for totally 7 days. Standard supportive care will be done for both groups similarly.

Trial Identifier/registry ID(s)/contact	ClinicalTrial.gov: NCT04411433 Contact: Prof. Ateş Kara; +90 532 4135130; ateskara@hacettepe.edu.tr	ClinicalTrial.gov: NCT04319900 ChiCTR2000030987 Other trial ID: 2020-K-24-2 Contact: Shumin Wang; +86 13488760399; shuminwang7000@163.com	Iranean registry of Randomised Trials (IRCT) ID: IRCT20151227025726N14 Contact: Farzaneh Dastan; +98 21 8820 0118; f_dastan@sbmu.ac.ir
	Trial arm 6: • Hydroxychloroquine, 400 mg bid on day 1, 200 mg bid for on day 2 to 5 combined with Azithromycin 500 once on day 1, 250 mg once on day 2 to 5, oral intake		
Comparator (standard care or generic drug name and dosage)	Any of the active components above	Placebo: • schedule not described	Lopinavir-ritonavir arm: • Lopinavir-ritonavir (Heterd company, India) at dose of 200/50 mg two tablets BID for 7 days. Standard supportive care will be done for both groups similarly.
Primary Outcome(s)	• Time to recovery (discharge) up to 14 days • Decrease in viral load up to 14 days	• Time of Improvement or recovery of respiratory symptoms up to 10 days • Number of days virus nucleic acid shedding up to 10 days • Frequency of Improvement or recovery of respiratory symptoms up to 10 days	• Fever through day 14 • Cough through day 14 • Dyspnea through day 14
Sponsor/ lead institution, country (also country of recruitment if different)	Sponsor: Ministry of Health, Turkey	Beijing Chao Yang Hospital, China	Shahid Beheshti University of Medical Sciences, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-19 Ongoing phase 3 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	EudraCT ID: 2020-001528-32 Other ID: ARCO-Homestudy Contact: Simone Lanini	ClinicalTrials.gov ID: NCT04529499 Contact: Srinivas Shenoy; 609-955-0249; srinivasshenoyb@drreddys.com	JPRN-JapicCTI-205238 [29] Contact: FUJIFILM Toyama Chemical Co., Ltd. Development Coordination Department
Study design, study phase	Phase 3 Multicenter, 5-arm randomized open label controlled trial with adaptive design	Phase 3 Multicenter, 2-arm randomized double blind placebo controlled trial with parallel group assignment. Blinding of	Phase 3 Multicenter, Adaptive, Randomized, Placebo-Controlled, Comparative Study

Trial Identifier/registry ID(s)/contact	EudraCT ID: 2020-001528-32 Other ID: ARCO-Homestudy Contact: Simone Lanini	ClinicalTrials.gov ID: NCT04529499 Contact: Srinivas Shenoy; 609-955-0249; srinivasshenoyb@drreddys.com	JPRN-JapicCTI-205238 [29] Contact: FUJIFILM Toyama Chemical Co., Ltd. Development Coordination Department
		participants, care providers, investigators and outcomes Assessors.	
Recruitment status	Ongoing (last update at registry on 24 June 2020)	Active, not recruiting (last update at registry on 3 Feb. 2021)	Ongoing, recruitment completed (last update at registry 1 Sept. 2020)
Number of Patients, Disease severity*	Minimal 175 to maximal 435 (adaptive design) Symptomatic, not meeting criteria for immediate hospitalization (national early warning score-NEWS = 2 criteria)	780 Moderate to severe	96 Patients with COVID-19 non-severe pneumonia
Setting (hospital, ambulatory,..)	Ambulatory	quarantined in an institutional quarantine facility or hospitalised	Hospitalised
Intervention (generic drug name and dosage)	• Trial arm darunavir/cobicistat (Rezolsta, Janssen-Cilag) 800/150 mg SID for 14 days • Trial arm idrossiclorochina (plaquenil, Sanofi-Aventis) 400 mg BID on day 1, 200 mg BID on day 2 to 10 • Trial arm lopinavir/ritonavir (Kaletra, AbbVie) 400/100 mg BID for 14 days • Trial arm favipiravir (avigan, Fujifilm) 1.800 mg BID on day 1, 800 mg BID on day 2 to 10	favipiravir (Avigan 200 mg tablets) + supportive care: 1,800 mg BID on Day 1 + 800 mg BID for next 9 days (maximum) & supportive care based on investigator's judgement and as per individual patient's requirement.	Favipiravir (T-705), Oral Multiple Dose, not further defined & standard care
Comparator (standard care or generic drug name and dosage)	• Trial arm: no antiviral treatment	Placebo for 10 days using the same dosing shedule as used in the interventional arm & supportive care as described above	Standard care, not further defined
Primary Outcome(s)	• Proportion of participants with undetectable SARS-CoV-2 gene E and gene M at day 7 after randomization. • Proportion of participants who need not hospitalization (NEWS = 2) by day 14 after randomization.	• Time to resolution of hypoxia (Stage I) [Time Frame: 1-28 days]: the earliest time point at which the patient has attained a score of 4 or lower on the 10-point ordinal scale of clinical status used by WHO in the SOLIDARITY trial (maintaining a blood oxygen saturation of ≥ 95% at rest on room air at sea level) when evaluated over a period of 24 hours.	• Time to alleviation of body temperature • Time to alleviation of SpO2 • Time to alleviation of chest image findings • time to SARS-CoV-2 RT-PCR negativity
Sponsor/ lead institution, country (also country of recruitment if different)	Istituto Nazionale Per Le Malattie Infettive (INMI) "Lazzaro Spallanzani" – Rom, Italy	Dr. Reddy's Laboratories Limited Recruitment in Kuwait	FUJIFILM Toyama Chemical Co., Ltd., Japan

Trial Identifier/registry ID(s)/contact	EudraCT ID: 2020-001528-32 Other ID: ARCO-Homestudy Contact: Simone Lanini	ClinicalTrials.gov ID: NCT04529499 Contact: Srinivas Shenoy; 609-955-0249; srinivasshenoyb@drreddys.com	JPRN-JapicCTI-205238 [29] Contact: FUJIFILM Toyama Chemical Co., Ltd. Development Coordination Department

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-20 Ongoing phase 3 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04558463 Contact: Dante S Harbuwono; +62213907703; dante.saksono@ui.ac.id	EudraCT ID: 2020-002728-35 Sponsor Protocol Number: HUN-AVI-01 Contact: CRO AdWare Research Ltd.; +36205967957; krisztina.hracs@adwareresearch.com	ClinicalTrials.gov ID: NCT04694612 Contact: Prabhat Adhikari; +977-9843003527; prabhatadhikari@gmail.com
Study design, study phase	Phase 3 Two arm open label randomized controlled trial with parallel group assignment	Phase 3 Two arm open label multicenter randomized controlled trial with parallel group assignment	Two-arm open label RCT with parallel group assignment. Phase 3 Computer based stratified block randomization with block size of 30. Concealment: independent and central randomization. Blinding: reported as open label with no blinding.
Recruitment status	Recruiting (last update at registry on 22 Sept. 2020)	Ongoing (last update at registry on 13 Aug. 2020)	Recruiting (last update at trial registry at 5 Jan 2021)
Number of Patients, Disease severity*	100 (planned) COVID-19 patients with mild, moderate and severe symptoms	150 COVID-19 with mild pneumonia.	N=676 Mild to moderate
Setting (hospital, ambulatory,..)	Hospital	Not described	Not reported
Intervention (generic drug name and dosage)	Favipiravir (avigan) plus standard care: • Favipiravir: 1600 mg twice a day (3200 mg/day) on day 1, 600 mg twice a day (1200 mg/day) on day 2 to 7 plus • Standard therapy consising of azithromycin 500 mg/day or levofloxacin 750 mg/day for 5 days, chloroquine (either Sulphur-based chloroquine 600 mg/day or chloroquine phosphate 100 mg/day or	Favipiravir (avigan): use of 200 mg tablets for oral use, dosage and duration not described	Favipiravir (Favir 200) • In mild COVID-19 patients: 1800 mg favipiravir po BID on day 1, then 800 mg po BID from day 2 to day 5 In moderate COVID-19 patients: favipiravir treatment of 1800 mg po BID on day 1, then 800 mg po BID from day 2 to 10

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04558463 Contact: Dante S Harbuwono; +62213907703; dante.saksono@ui.ac.id	EudraCT ID: 2020-002728-35 Sponsor Protocol Number: HUN-AVI-01 Contact: CRO AdWare Research Ltd.; +36205967957; krisztina.hracs@adwareresearch.com	ClinicalTrials.gov ID: NCT04694612 Contact: Prabhat Adhikari; +977-9843003527; prabhatadhikari@gmail.com
	hydroxychloroquine 400 mg/day) for 5-7 days, vitamin C, oxygen therapy according to the patients clinical condition, comorbid therapy and other symptomatic treatment such as antipyretic drug		
Comparator (standard care or generic drug name and dosage)	Oseltamivir plus standard care: • Oseltamivir, 75 mg bid (150 mg/day) for 7 plus standard care as described above	Supportive care: • described as symptomatic therapy	Placebo / remdesivir • In mild COVID-19 patients: 1800 mg placebo po BID on day 1, then 800 mg po BID from day 2 to day 5 In moderate COVID-19 patients: Inj Remdesivir 200 mg IV on day 1, followed by 100 mg IV daily up to day 5
Primary Outcome(s)	• Improvement of radiology results • RT PCR negative conversion during follow up	• Time to improvement in body temperature, SpO2, chest imaging findings and negative SARS-CoV-2. Timepoints of evaluation: days 4,7,10,13,16,19,22,25,28.	• clinical improvements ○ in mild cases [Time Frame: 5 day]: time to clinical improvements is defined as recovery in two out of the three common symptoms that includes fever (body temperature more than 99.5 degrees F), cough, and headache/malaise (scored more than 3 in a pain likert scale of 1 to 10). In moderate cases [Time Frame: 10 days]: Time to clinical improvement defined as Improvement in at least 2 out 3 selected common symptoms as above as in mild cases PLUS improvement in shortness of breath (*For the assessment of clinical improvement in moderate cases, we did not include imaging findings because radiological changes lag behind clinical improvement by a few weeks.)
Sponsor/ lead institution, country (also country of recruitment if different)	Indonesia University, Indonesia	Hungarian Ministry of Innovation and Technology - Representative: Hecrin Consortium; Hungary	Sponsor: Nepal Health Research Council

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04558463 Contact: Dante S Harbuwono; +62213907703; dante.saksono@ui.ac.id	EudraCT ID: 2020-002728-35 Sponsor Protocol Number: HUN-AVI-01 Contact: CRO AdWare Research Ltd.; +36205967957; krisztina.hracs@adwareresearch.com	ClinicalTrials.gov ID: NCT04694612 Contact: Prabhat Adhikari; +977-9843003527; prabhatadhikari@gmail.com

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-21 Ongoing phase 3 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04600895 Other Study ID Numbers: PRESECO Contact: Neil Patel; 561-351-7822; npatel@elixiacrc.com	ClinicalTrials.gov ID: NCT04600999 Other Study ID Numbers: HUN-AVI-01 Contact: Krisztina Hrács; 205967957 ext +36; krisztina.hracs@adwareresearch.com	IRCT20201028049175N1 Contact: Alireza Kamali; 086-32222003-8; alikamaliir@yahoo.com
Study design, study phase	Phase 3 Triple blinded two-arm open label randomized controlled trial with parallel group assignment. Masking of participant, care provider and investigator.	Phase 3 Multicenter two-arm open label randomized controlled trial with parallel group assignment.	Phase 3 Multicenter two-arm double blinded randomised placebo controlled trial with parallel group assignment Masking: participant and data analyst. permuted balanced block randomization method with the size of blocks 4 and 6. Random sequence will be generated by an epidemiologist by running an online program in sealed envelope website (https://www.sealedenvelope.com/). Concealment is also guaranteed due to the use of permuted balanced block randomization method.
Recruitment status	Recruiting (last update at registry on 17 Dec. 2020)	Recruiting (last update at registry on 23 Oct. 2020)	Recruiting (last update at registry at 12 Dec. 2020)
Number of Patients, Disease severity*	826 mild-moderate COVID-19 patients	150 Moderate COVID-19 patients with mild pneumonia	114 Moderate to severe
Setting (hospital, ambulatory,..)	Ambulatory	Hospital	Hospital
Intervention (generic drug name and dosage)	Favipiravir (Avigan): dosing shedule not reported	Favipiravir (avigan) plus supportive care Favipiravir: 1800 mg bid (total 3600 mg) on day 1, 800 mg bid (total 1600 mg) on day 2 to 14.	Favipiravir: 1600 mg twice daily on first day and: 600 mg twice daily on days 2–7.

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04600895 Other Study ID Numbers: PRESECO Contact: Neil Patel; 561-351-7822; npatel@elixiacrc.com	ClinicalTrials.gov ID: NCT04600999 Other Study ID Numbers: HUN-AVI-01 Contact: Krisztina Hrács; 205967957 ext +36; krisztina.hracs@adwareresearch.com	IRCT20201028049175N1 Contact: Alireza Kamali; 086-32222003-8; alikamaliir@yahoo.com
Comparator (standard care or generic drug name and dosage)	Placebo	Supportive care, defined as symptomatic therapy.	Placebo for 7 days
Primary Outcome(s)	Time to sustained clinical recovery over a consecutive period of 48 hours. Time Frame: from day 0 to day 21.	• Time to improvement in body temperature Time Frame: 9 months • Time to improvement in SpO2. Time Frame: 9 months • Time to improvement in chest imaging findings. Time Frame: 9 months Time to improvement in negative SARS-CoV-2. Time Frame: 9 months	• Severity of coronavirus 2019: before prescription of drug and then every day until 7 days, measured with pulse oximetry, resspiratory rate, heart rate, CT scan
Sponsor/ lead institution, country (also country of recruitment if different)	Sponsor Appili Therapeutics Inc., USA	University of Pecs, Hungary	Arak University of Medical Sciences, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
For abbreviations see “List of abbreviations” at page 5

Table 4-22 Ongoing phase 3 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	IRCT20171219037964N3 Contact: Babak Amra; +98 31 3668 0048; Amra@med.mui.ac.ir	CTRI/2020/06/025799 Contact: Dr Sandesh Sawant; 022-23025193; sandesh.sawant3@cipla.com	Iranian Registry of Clinical Trials ID: IRCT20201005048936N1 Contact: Ayat Ahmadi at aahmadi@tums.ac.ir, telephone: +98 21 8897 5660
Study design, study phase	Phase 3 Multicenter two-arm triple blinded randomised placebo controlled trial with parallel group assignment Masking: patient, care povider, investigator, outcome assessor and data analyzer simple randomization via www.randomization.com: each patient will be assigned with a number by the physician. then this number will be matched by the random string by	Phase 3 Multicenter two-arm open label randomised controlled trial with parallel group assignment Masking: none Computer generated randomization with centralized allocation	Phase 3 Two-arm open label RCT with parallel group assignment. Blinding: none; randomization using , There is no concealment over the randomization process

Trial Identifier/registry ID(s)/contact	IRCT20171219037964N3 Contact: Babak Amra; +98 31 3668 0048; Amra@med.mui.ac.ir	CTRI/2020/06/025799 Contact: Dr Sandesh Sawant; 022-23025193; sandesh.sawant3@cipla.com	Iranian Registry of Clinical Trials ID: IRCT20201005048936N1 Contact: Ayat Ahmadi at aahmadi@tums.ac.ir, telephone: +98 21 8897 5660
	research assistant and the patient will be assigned to group A or B according to that		
Recruitment status	Recruiting (last update at registry at 2 Dec. 2020)	Not yet recruiting	Recruiting (last update at trial registry at 26 October 2020)
Number of Patients, Disease severity*	70 Mild-moderate	156 mild to moderate COVID-19	N=126 Mild to moderate
Setting (hospital, ambulatory,..)	Ambulatory	Hospital	Hospital
Intervention (generic drug name and dosage)	Favipiravir 200 mg, 8 pills (2 pills, 4 times a day) for 5 days	Favipiravir With Supportive Care: • Favipiravir 1800 mg twice daily on Day 1 and 800 mg twice daily from day 2 to 14 (maximum) along with supportive care	N= 63 Favipiravir administered orally (Dr. Abidi pharmaceutical Co), 3200mg (1600mg/ bid) on the first day followed by 1200mg (600mg/bid) daily for the next 4 days (days 1-5).
Comparator (standard care or generic drug name and dosage)	placebo, 8 pills daily for 5 days	Supportive care: • Not described	N=63 Control group: Hydroxichloroqune 400mg (bid) on the first day, followed by 200mg/day (bid) for the next 4 days (days 1-5) with or without Naproxen and with or without Azythromycin
Primary Outcome(s)	Treatment failure at days 3, 7, 14, 21, 28 from the start of treatmen, measured with patient interviews.t	Time from randomization to negativity in RT-PCR nucleic acid test, defined as the presence of two consecutive negative results with RT-PCR detection over an interval of 24 hour. Time frame: Till discharge/death whichever is earlier (up to Day 28).	• Proportion of patients with negative test results in the 6th and the 14th day of follow up • Time to symptoms recovery (fever, cough) up to 14 days follow up • Proportion of patients with recovered symptoms on the 28th day follow up
Sponsor/ lead institution, country (also country of recruitment if different)	Esfahan University of Medical Sciences, Iran	Cipla Ltd, India	Sponsor: Dr. Abidi pharmaceutical Co, Tehran, Iran. Lead institution: Tehran University of Medical Sciences, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
For abbreviations see “List of abbreviations” at page 5

Table 4-23 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04464408 Acronym: Avi-Mild Contact: Mohammad Bosaeed; +966(11)8011111; dr.bosaeed@live.com	ClinicalTrials.gov ID: NCT04448119 Other ID: CONTROL-COVID-Favipiravir-1 Contact: Allison J McGeer; +1 416-586-3123; Allison.McGeer@sinaihealth.ca
Study design, study phase	Phase 2, Phase 3 Two-arm randomized controlled trial with parallel group assignment Masking: Triple (Participant, Investigator, Outcomes Assessor)	Phase 2, early treatment/prophylaxis Two-arm randomized controlled trial with parallel group assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Recruitment status	Recruiting (last update at trial registry 9 Sept. 2020)	Recruiting (last update at trial registry 23 Oct. 2020)
Number of Patients, Disease severity*	578 Mild COVID-19	760 Not described, likely from no disease to severe disease
Setting (hospital, ambulatory,..)	Not described	Long-term care homes
Intervention (generic drug name and dosage)	Favipiravir: 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily (Maximum days of therapy is 7 days)	Favipiravir (Avigan): 1600 mg (8 x 200 mg tablets) orally twice daily on day 1 followed by 800 mg (4 x 200 mg tablets) orally twice daily on days 2-25. The dose of favipiravir for treatment is 2000 mg orally twice daily on day 1, the 1000 mg orally twice daily for 13 additional days
Comparator (standard care or generic drug name and dosage)	Placebo: 9 tablets by mouth twice daily for one day, followed by 4 tablets twice daily (Maximum days of therapy is 7 days)	Placebo: 8 tablets orally twice daily on day 1, followed by 4 tablets twice daily from days 2-25. The dosage of favipiravir placebo for treatment is 10 tablets orally twice daily on day 1, followed by tablets twice daily from days 2-14
Primary Outcome(s)	Primary efficacy outcome: • PCR negative [Time Frame: 15 days]	Primary efficacy outcome: Control of Outbreak [Time Frame: Day 40]
Sponsor/ lead institution, country (also country of recruitment if different)	King Abdullah International Medical Research Center, Saudi Arabia	Appili Therapeutics Inc.

Table 4-24 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04358549 Other Ids: FAVI-COV-US201 Contact: see sponsor information	ClinicalTrials.gov ID: NCT04387760 Other Ids: 40 / 07-May-2020 Contact: Manaf Al Qahtani; +97339766000; mqahtani@rcsi-mub.com	ClinicalTrials.gov ID: NCT04434248 [9]** Other Ids: COVID-FPR-01 Contact: Andrey A Ivashchenko; ai@chemrar.ru
Study design, study phase	Phase 2 Open label, randomized (1:1 ratio), controlled, multicenter Phase 2 proof-of-concept study, with parallel group assignment	Phase 2 Randomized open label randomized controlled trial with parallel group assignment	Phase 2/3, Adaptive, multicenter, open-label, randomized clinical study (Sequential Assignment)
Recruitment status	Active, not recruiting (last update at trial registry 5 Feb. 2021)	Recruiting (last update at trial registry 18 Aug. 2020)	Active, not recruiting (last update at trial registry 16 June 2020)
Number of Patients, Disease severity*	50 (actual) Not described	150 Mild to moderate COVID-19	330 Moderate to severe COVID-19
Setting (hospital, ambulatory,..)	Inpatients	Inpatients	Inpatients
Intervention (generic drug name and dosage)	Favipiravir 1800 mg BID plus Standard of Care (SOC) Days 2-14: 1000 mg BID plus SOC. For subjects with Child-Pugh A liver impairment: Days 2-14: 800 mg BID plus SOC	Favipiravir/Avigan/T-705/Favipira/favilavir: 1600mg BID PO day 1, 600mg BID PO day 2 to 10. In addition to Favipiravir all patients will receive the standard care (according to local Bahrain COVID19 guidelines). Any patient who is fit for discharge, can be discharged and medications will be stopped on discharge	Favipiravir/ Avifavir: Pilot stage: Favipiravir (200 mg coated tablets) 1600 mg twice a day (BID) on Day 1 followed by 600 mg BID on Days 2-14 (1600/600 mg), or Favipiravir (200 mg coated tablets) 1800 mg BID on Day 1 followed by 800 mg BID on Days 2-14 Pivotal stage: Favipiravir, the dose will be selected based on pilot study results
Comparator (standard care or generic drug name and dosage)	Standard of Care for 14 days	Hydroxychloroquine/Hydroxychloroquine sulfate/Plaquenil: 400mg BID PO day 1 then 200mg BID PO from day 2-day 10. In addition to Hydroxychloroquine all patients will receive the standard care (according to local Bahrain COVID19 guidelines). Any patient who is fit for discharge, can be discharged and medications will be stopped on discharge	Pilot stage: standard of care, based on approved clinical recommendations for treatment of COVID-19 in the Russian Federation (but not Favipiravir). Might include hydroxychloroquine, chloroquine, lopinavir/ritonavir or other recommended schemes.
Primary Outcome(s)	• Time to viral clearance [Time Frame: Day 29]	• Primary outcome measure will be time to viral clearance [Time Frame: Until discharge or for a maximum of 14 days or readmission]	• Rate of viral elimination by Day 10 [pilot stage, dose selection] [Time Frame: 10 Days] • Time to viral elimination [pivotal stage] [Time Frame: 28 Days] • Time to clinical improvement [pivotal stage] [Time Frame: 28 Days]

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04358549 Other Ids: FAVI-COV-US201 Contact: see sponsor information	ClinicalTrials.gov ID: NCT04387760 Other Ids: 40 / 07-May-2020 Contact: Manaf Al Qahtani; +97339766000; mqahtani@rcsi-mub.com	ClinicalTrials.gov ID: NCT04434248 [9]** Other Ids: COVID-FPR-01 Contact: Andrey A Ivashchenko; ai@chemrar.ru
Sponsor/ lead institution, country (also country of recruitment if different)	Fujifilm Pharmaceuticals U.S.A., Inc.	Royal College of Surgeons in Ireland - Medical University of Bahrain, Bahrain	Chromis LLC, Russia

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19; ** Interim report published [9], status 14 Oct. 20. Outcome data from the interim report are included in the Summary of Findings Table 4-1

Abbreviations: see "List of abbreviations" at page 5.

Table 4-25 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04346628 Contact: Yvonne (Bonnie) A Maldonado; Stanford University	ClinicalTrials.gov ID: NCT04402203 Contact: Ahmedul Kabir; +88 01720910541; ahmedul_986@yahoo.com	ClinicalTrials.gov ID: NCT04445467 [30] Acronym: VIRCO Contact: Janine Roney; +61 3 9076 6908 gaclinresearch@alfred.org.au
Study design, study phase	Phase 2, early treatment Randomized double blinded placebo controlled trial with parallel group assignment	Phase 2, treatment Multicenter double-blind, placebo-controlled randomized control study with parallel group assignment	Phase 2, treatment Adaptive randomized controlled trial with parallel group assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Recruitment status	Enrolling by invitation (last update at trial registry 2 Oct. 2020)	Recruiting (last update at trial registry 26 May 2020)	Recruiting, (last update at trial registry 19 Aug. 2020)
Number of Patients, Disease severity*	120 Mild or asymptomatic COVID-19	50 Mild to moderate COVID-19	190 Not described
Setting (hospital, ambulatory,..)	Not described	Inpatients	In and outpatients
Intervention (generic drug name and dosage)	In addition to SOC, Favipiravir administered orally, 1800 mg on the first dose (day 1) followed by 800 mg twice daily for the next 9 days (days 2-10)	Favipiravir 200 mg (Favipira) tablet will be given orally. Day 1: Tablet Favipiravir 1600 mg twice daily Days 2−Days 10: Tablet Favipiravir 600 mg twice daily	Favipiravir 1800 mg twice daily on Day 1 followed by 800 mg Favipiravir twice daily for the next 13 days
Comparator (standard care or generic drug name and dosage)	In addition to SOC, placebo to match favipiravir for 10 days	Standard Treatment	Placebo
Primary Outcome(s)	• Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days]	• Number of participants negative by RT-PCR for the virus at 4-10 days after initiation of therapy. [Time Frame: at 4 to 10 days of therapy] • Number of participants with lung condition change assessed with X-ray.	• Time to virological cure [Time Frame: 14 days]

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04346628 Contact: Yvonne (Bonnie) A Maldonado; Stanford University	ClinicalTrials.gov ID: NCT04402203 Contact: Ahmedul Kabir; +88 01720910541; ahmedul_986@yahoo.com	ClinicalTrials.gov ID: NCT04445467 [30] Acronym: VIRCO Contact: Janine Roney; +61 3 9076 6908 gaclinresearch@alfred.org.au
		[Time Frame: at Day-4, Day-7 and Day-10 of therapy]	
Sponsor/ lead institution, country (also country of recruitment if different)	Stanford University, United States	Bangladesh Medical Research Council (BMRC), Bangladesh	Bayside Health, Australia

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-26 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04310228* [16] Chinese Clinical Trial Registry ID: ChiCTR2000030894 Contact: Hong Zhao; 13810765943; zhaohong_pufh@bjmu.edu.cn	EudraCT Number: 2020-001904-41 [31] ISRCTN ID: ISRCTN31062548 Trial acronym: GETAFIX Contact: Janet Scott; janet.scott@glasgow.ac.uk.	EudraCT number: 2020-002106-68 ClinicalTrials.gov ID: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals Contact: FLARE Trial Team UCL CCTU; +44 20 3108 9840; cctu.flare@ucl.ac.uk
Study design, study phase	Phase not described Multicenter three-arm open label randomized controlled trial with parallel group assignment	Phase 2 Single center two-arm randomised placebo* controlled trial in parallel design. * Although the trial was described as placebo controlled, it was also described as open trial, so that the masking method is unclear.	Phase 2 Multicenter, randomised, double-blind, 2x2 factorial placebo-controlled trial Masking: triple (participant, care provider, investigator)
Recruitment status	Recruiting (last update at trial registry 10 April 2020)	Ongoing, recruiting (last update at trial registry 24 Sept. 20)	Recruiting (last update at trial registry 30 Oct. 2020)
Number of Patients, Disease severity**	150 Not described, cases of respiratory failure and requiring mechanical ventilation were excluded	302 Point 1, 2, 3, or 4 on the WHO COVID-19 ordinal severity scale at time of randomisation. (Asymptomatic with positive COVID19 test, Symptomatic Independent, Symptomatic assistance needed, Hospitalized, with no oxygen therapy) Have >=10% risk of death should they be admitted to hospital as defined by the ISARIC4C risk index: https://isaric4c.net/risk	240 Non-severe, non-critical. Focus on early manifestations of disease: symptoms compatible with COVID-19 disease within the first 7 days of symptom onset before enrolment or asymptomatic persons who tested positive with SARS-CoV-2 within the last 48 hours before enrolment

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04310228* [16] Chinese Clinical Trial Registry ID: ChiCTR2000030894 Contact: Hong Zhao; 13810765943; zhaohong_pufh@bjmu.edu.cn	EudraCT Number: 2020-001904-41 [31] ISRCTN ID: ISRCTN31062548 Trial acronym: GETAFIX Contact: Janet Scott; janet.scott@glasgow.ac.uk.	EudraCT number: 2020-002106-68 ClinicalTrials.gov ID: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals Contact: FLARE Trial Team UCL CCTU; +44 20 3108 9840; cctu.flare@ucl.ac.uk
Setting (hospital, ambulatory,..)	Not described	In and outpatients	Not described, likely outpatients
Intervention (generic drug name and dosage)	Favipiravir group: • 1600 mg BID on day 1; 600mg BID on day 2-7 (maximum). Oral administration. Favipiravir Combined With Tocilizumab group: • Favipiravir: 1600 mg BID on day 1, 600 mg BID on day 2-7 (maximum). Oral administration. Tocilizumab: The first dose is 4 ~ 8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg	Avigan, 200 mg for maximum of 10 days, oral intake. In addition to standard care	Trial arm with single agent: • Avigan (Favipiravir) 200 mg daily • Trial arm with single agent: Kaletra (Lopinavir/ritonavir), 200/50 mg daily, oral intake Trial arm with combination therapy: • Avigan (Favipiravir) 200 mg daily + Kaletra (Lopinavir/ritonavir) 200/50 mg daily, oral intake
Comparator (standard care or generic drug name and dosage)	• Tocilizumab group: the first dose is 4 ~ 8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg.	Standard of care	• Matched Placebo, oral intake, dosing scheme and mg identical to Avigan and Kaletra schemes.*
Primary Outcome(s)	• Clinical cure rate at 3 months (trial registration site) • Cumulative lung lesion remission rate: lung CT examination indicated absorption of lung inflammation (published report)	• reduction in disease severity defined as clinical status as assessed by WHO COVID 10 point ordinal severity scale at day 15.	• upper respiratory tract viral load at Day 5 as measured with quantitative polymerase chain reaction (PCR) performed on saliva samples

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04310228* [16] Chinese Clinical Trial Registry ID: ChiCTR2000030894 Contact: Hong Zhao; 13810765943; zhaohong_pufh@bjmu.edu.cn	EudraCT Number: 2020-001904-41 [31] ISRCTN ID: ISRCTN31062548 Trial acronym: GETAFIX Contact: Janet Scott; janet.scott@glasgow.ac.uk.	EudraCT number: 2020-002106-68 ClinicalTrials.gov ID: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals Contact: FLARE Trial Team UCL CCTU; +44 20 3108 9840; cctu.flare@ucl.ac.uk
Sponsor/ lead institution, country (also country of recruitment if different)	Peking University First Hospital, China	NHS Greater Glasgow and Clyde / The University of Glasgow, UK	University College London Comprehensive Clinical Trial Unit, UK

* An interim report has been published, outcome data are included in Table 4.4, Table 4.5 and Table 4.6 [16]; **Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Abbreviations: see "List of abbreviations" at page 5.

Table 4-27 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04333589 Contact: Guiqiang Wang; 13911405123; john131212@sina.com	ClinicalTrials.gov ID: NCT04351295 Contact: Sherief Abd-Elsalam; 00201147773440; sheriefabdelsalam@yahoo.com	Thai Clinical Trial Registry: TCTR20200514001 Contact: unclear, website was inaccessible
Study design, study phase	Not described Multicenter randomized open label controlled trial with parallel group assignment	Phase 2/3 Multicenter randomized open label controlled trial with parallel group assignment	Phase 2 / 3 Two-arm open-label randomized placebo controlled trial with parallel group assignment
Recruitment status	Recruiting (last update at trial registry: 24 April 2020)	Recruiting (last update at trial registry: 29 Sept. 2020)	Pending, not yet recruiting (last updated at trial registration: 13 May 2020)
Number of Patients, Disease severity*	210 Not described	90 Not described	96 Mild or moderate COVID-19
Setting (hospital, ambulatory,..)	Not described	Not described	Not described
Intervention (generic drug name and dosage)	Favipiravir group On the 1st day, 1600 mg BID on day 1, 600 mg BID on day 2-7. Oral administration, the maximum number of days taken is not more than 14 days	Faviprevir, not further described	Favipiravir: supportive care + favipiravir 1800 mg bid on day 1, 800 mg bid on day 2-5 (minimum) or day 2-13 (maximum)
Comparator (standard care or generic drug name and dosage)	Regular treatment group	Placebo	Supportive care: symptomatic therapy not further defined for 4 days (maximum)
Primary Outcome(s)	Viral nucleic acid test negative conversion rate [Time Frame: 5 months]	Number of patients with mortality or need for mechanical ventilation	Time to improvement in body temperature and SpO2 without chest imaging findings, and negative SARS-Cov2 through day 28
Sponsor/ lead institution, country (also country of recruitment if different)	Peking University First Hospital, China	Tanta University, Egypt	Faculty of Medicine, Siriraj Hospital, Thailand

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04333589 Contact: Guiqiang Wang; 13911405123; john131212@sina.com	ClinicalTrials.gov ID: NCT04351295 Contact: Sherief Abd-Elsalam; 00201147773440; sheriefabdelsalam@yahoo.com	Thai Clinical Trial Registry: TCTR20200514001 Contact: unclear, website was inaccessible

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-28 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	Chinese Clinical Trial Registry ID: ChiCTR2000029548 Contact: Yunqing Qiu; +86 13588189339; qiuyq@zju.edu.cn	Chinese Clinical Trial Registry ID: ChiCTR2000030113 Contact: Liu Yingxia; +86 755 61238922; yingxialiu@hotmail.com	Chinese Clinical Trial Registry ID: ChiCTR2000029996 Contact: Zhaohui Tong; +86 13910930309
Study design, study phase	Three arm randomized open label controlled trial with parallel group assignment	Two arm randomized open label controlled trial with parallel group assignment. Stratified randomization by disease severity.	Phase 2 Three arm randomized open label controlled trial with parallel group assignment
Recruitment status	Not yet recruiting (registration last updated at 12 Feb. 2020)	Recruiting (registration last updated at 24 Feb. 2020)	Recruiting (registration last updated at 12 Feb. 2020)
Number of Patients, Disease severity*	30 non-severe COVID-19 adults with pneumonia who tested positive for novel coronavirus infection after the onset of symptoms using a real time polymerase chain reaction (RT-PCR)-based diagnostic assay	30 Any, corona pneumonia with poorly responsive ritonavir Randomised to ritonavir or favipiravir	60 with pneumonia: „ inpatient diagnosed with Novel coronavirus pneumonia diagnosed and clinical classification of ordinary type: Inpatients with fever (underarm temperature >= 37.0 degree C), respiratory tract, etc. Imaging shows pneumonia"
Setting (hospital, ambulatory,..)	Not described	Not described, likely hospitalised	Hospitalised
Intervention (generic drug name and dosage)	Trial arm: "Favipiravir 600 mg tid with 1600 mg first loading dosage for no more than 14 days."	Favipiravir, not further described	Fapilavir tablets (Favilavir was formerly called Fapilavir, approved by China for covid-19 treatment by February 17, 2020) • Low dose trial arm: tablets; 200mg; oral; twice a day; The adult dose is 1600 mg per time on first day; the duration of treatment will be 10 d. • Middle dose trial arm: tablets; 200mg; orally; twice a day;The adult dose is 1800 mg per time on first day; the duration of treatment will be 10 d. • High dose trial arm: tablets; 200mg; oral; twice a day; The adult dose is

Trial Identifier/registry ID(s)/contact	Chinese Clinical Trial Registry ID: ChiCTR2000029548 Contact: Yunqing Qiu; +86 13588189339; qiuyq@zju.edu.cn	Chinese Clinical Trial Registry ID: ChiCTR2000030113 Contact: Liu Yingxia; +86 755 61238922; yingxialiu@hotmail.com	Chinese Clinical Trial Registry ID: ChiCTR2000029996 Contact: Zhaohui Tong; +86 13910930309
Study design, study phase	Three arm randomized open label controlled trial with parallel group assignment	Two arm randomized open label controlled trial with parallel group assignment. Stratified randomization by disease severity.	Phase 2 Three arm randomized open label controlled trial with parallel group assignment
Recruitment status	Not yet recruiting (registration last updated at 12 Feb. 2020)	Recruiting (registration last updated at 24 Feb. 2020)	Recruiting (registration last updated at 12 Feb. 2020)
			2400 mg per time on first day; the duration of treatment will be 10 d.
Comparator (standard care or generic drug name and dosage)	Trial arm: Baloxavir Marboxil 80 mg on day 1, 80 mg on day4; and 80 mg on day 7 as necessary. No more than 3 times administration in total. Trial arm: Lopinavir-Ritonavir "2# (200 mg / 50 mg), tid, for 14days."	Keep ritonavir/ritonavir treatment	See above
Primary Outcome(s)	• Time to viral negativity by RT-PCR • Time to clinical improvement: Time from start of study drug to hospital discharge or to NEWS2<2 for 24 hours."	• "Blood routine tests, Liver function examination, Renal function examination, Blood gas analysis, Chest CT examination"	• Time to Clinical Recovery defined as normal body temperature and cough relief • "Observation until discharge or turn to severe"
Sponsor/ lead institution, country (also country of recruitment if different)	The First Affiliated Hospital, Zhejiang University School of Medicine, China	The Third People's Hospital of Shenzhen, China	Beijing Chaoyang Hospital, Capital Medical University, China

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-29 Ongoing phase 2 trials of single agents: Favipiravir, continued

Trial Identifier/registry ID(s)/contact	Chinese Clinical Trial Registry ID: ChiCTR2000030254* [14] Contact: Xinghuan Wang; +86 027 67813096; wangxinghuan@whu.edu.cn	Iranian Registry of Clinical Trials ID: IRCT20150808023559N23 Contact: Somaieh Matin at s.matin@arums.ac.ir; Ardabil University of Medicine Sciences, Iran; telephone +98 45 3373 3011	
Study design, study phase	Phase not specified Multicenter randomised, open label, controlled trial with parallel group assignment.	Two-arm open label RCT with parallel group assignment. Phase 2 Blinding: none	
Recruitment status	Recruitment completed	Recruitment complete (last update at trial registry at 11 October 2020)	
Number of Patients, Disease severity**	240 Not reported. Severe patients with expected survival time < 48 hours are excluded	100 Moderate to severe COVID-19	
Setting (hospital, ambulatory,..)	Hospitalised	Hospital	
Intervention (generic drug name and dosage)	Favipiravir ("Farpiravir tablets"), not further described	N=50 Favipiravir. start dose of eight 200 mg Favipiravir tablets (Nafas farmed Co, Iran) followed by Favipiravir 600 mg three times a day for 7 days. This regimen could be continued for 10 days if necessary according to clinical response of the patient.	
Comparator (standard care or generic drug name and dosage)	Arbidol ("abidole tablets"), not further descibed	N=50 Tenofovir alafenamid (Bakhtar bioshimi Co, Iran) 25 mg for 7 days	
Primary Outcome(s)	Clinical recovery rate of day 7	Hospital mortality up to two weeks after the intervention. Method of measurement: Patient medical records.	
Sponsor/ lead institution, country (also country of recruitment if different)	Zhongnan Hospital of Wuhan University, China	Ardabil University of Medical Sciences, Iran Imam Khomeini Hospital, Ardabil, Iran	

* Published at preprint server, outcome data included in Table 4.2 [14]; ** Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-30 Ongoing observational studies of single agent favipiravir

Trial identifier/registry ID(s)/contact	CTRI/2020/11/029263 Contact: Saiprasad Patil; Saiprasad.Patil@glenmarkpharma.com	JPRN-jRCTs041200025 Acronym: J-CRITICAL trial Contact: Yuichiro Shindo; +81-52-741-2111; yshindo@med.nagoya-u.ac.jp	jRCTs031190226 Contact: Tokue Yutaka; +81-27-220-8549¸ tokue49@gmail.com
Study design, study phase	Prospective, Open label, Multicentre, Single Arm, Post Marketing study	Prospective, Open label, Single Arm study	Prospective multicenter open single arm trial
Recruitment status	Open to recruitment (last update at trial registry on 23 Dec. 2020)	Recruiting (last update at trial registry on 1 July 2020)	Recruiting (last update at trial registry on 28 Sept. 2020)
Number of Patients, Disease severity*	1200 Mild to moderate	69 COVID-19 pneumonia in need of oxygen therapy	100 Disease severity not reported, with or without pneumonia
Setting (hospital, ambulatory,..)	Likely Ambulatory	Hospital	Hospital
Intervention (generic drug name and dosage)	3600 mg (1800 mg orally twice daily) on 1st day followed by 800 mg orally twice daily, up to maximum of 14 days	Combination therapy with favipiravir and methylprednisolone, not further specified	Favipiravir not further specified
Comparator (standard care or generic drug name and dosage)	none	None	None
Primary Outcome(s)	• Number of AEs • Number of SAEs • Number of treatment related AEs and SAEs as assessed by the treating physician • Number of AEs leading to dose modification/discontinuation of treatment	• Proportion of patients who need mechanical ventilation or those who meet the criteria of tracheal intubation* within 14 days of initiation of treatment	• expected value and 95% CI of ratio of C-reactive protein before versus after the treatment
Sponsor/ lead institution, country (also country of recruitment if different)	Glenmark Pharmaceuticals Ltd, India	Nagoya University Hospital, Japan	Not reported, but likely Gunma University Hospital, Japan

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5

Table 4-31 Ongoing observational studies of single agent favipiravir

Trial identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04474457 Other ID: COVID-19-PMSFAV Contact: Prof. Ateş Kara; +90 532 4135130; ateskara@hacettepe.edu.tr
Study design, study phase	Phase not specified, observational Study Design: multicenter prospective observational cohort

Trial identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04474457 Other ID: COVID-19-PMSFAV Contact: Prof. Ateş Kara; +90 532 4135130; ateskara@hacettepe.edu.tr
Recruitment status	Active, not recruiting (last update at trial registry 1 February 2021)
Number of Patients, Disease severity*	1000 (actual) Not described
Setting (hospital, ambulatory,..)	Not described
Intervention (generic drug name and dosage)	Favipiravir
Comparator (standard care or generic drug name and dosage)	None
Primary Outcome(s)	Primary efficacy outcome: • Time to recovery (discharge) [Time Frame: 7 days] • Decrease in viral load [Time Frame: 7 days]
Sponsor/ lead institution, country (also country of recruitment if different)	Ministry of Health, Turkey

Table 4-32 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir

Trial Identifier/registry ID(s)/contact	NCT04359615 Trial acronym: FIC Contact: Seyed Sina Naghibi Irvani; +989141182825; sina.irvani@gmail.com	ClinicalTrial.gov: NCT04392973 Trial acronym: FACCT - FAvipiravir and HydroxyChloroquine Combination Therapy. Contact: Mohammad Bosaeed; +966(11)8011111; dr.bosaeed@live.com	ClinicalTrials.gov ID: NCT04376814 Contact: Mohammad Sadegh Bagheri Baghdasht; Baqiyatallah Medical Sciences University
Study design, study phase	Phase 3 (described by trial authors as phase 4) Single center 2-arm randomised triple blinded controlled trial with parallel group design	Phase not described Multicenter, open label, randomised controlled trial in parallel design	Phase not described Non-randomized open label controlled trial with parallel group assignment
Recruitment status	Not yet recruiting (last update at trial registry 28 April 2020)	Recruiting (last update at trial registry 28 July 2020)	Completed (last update at trial registry 16 June 2020)
Number of Patients, Disease severity*	40 Not described	520 Moderate or Severe COVID-19, defined as oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or significant clinical symptoms with	40 Not described, requiring hospitalization

Trial Identifier/registry ID(s)/contact	NCT04359615 Trial acronym: FIC Contact: Seyed Sina Naghibi Irvani; +989141182825; sina.irvani@gmail.com	ClinicalTrial.gov: NCT04392973 Trial acronym: FACCT - FAvipiravir and HydroxyChloroquine Combination Therapy. Contact: Mohammad Bosaeed; +966(11)8011111; dr.bosaeed@live.com	ClinicalTrials.gov ID: NCT04376814 Contact: Mohammad Sadegh Bagheri Baghdasht; Baqiyatallah Medical Sciences University
		Chest X ray changes that require hospital admission	
Setting (hospital, ambulatory,..)	Hospitalized	Hospitalised	Inpatients
Intervention (generic drug name and dosage)	Favipirair & Hydroxychloroquine, dose and route of administration not reported	Avigan (Favipiravir), 10 days: 1800 mg (9 tablets) orally twice daily at day 1, 800 mg (4 tablets) twice daily at day 2 to maximally day 10 or till hospital discharge + Hydroxychloroquine 5 days, 400 mg twice daily on day 1, 200 mg twice daily on day 2 to 5. Route of administration is oral or though nasogastric tube.	Faviprevir: at dose of 1600mg Favipiravir tablets for the first time, and for next time 600mg of favipiravir tablets three times per day for 7 days, plus 200mg of Hydroxychloroquine two times per day will be given to patients for 7 days.
Comparator (standard care or generic drug name and dosage)	Hydroxychloroquine, dose and route of administration not reported	Standard of care	• Hydroxychloroquine 400mg tablets two times per day • 200/50 mg of Lopinavir / Ritonavir (Kaletra) two times per day for seven days
Primary Outcome(s)	• Time to clinical improvement up to 14 days	• clinical improvement up to 28 days, defined as the time from the randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live discharge from the hospital, whichever came first.	• Mortality up to 28 days • long of hospitalization up to 28 days • Laboratory Treatment Response (Blood cell count) up to 28 days • Laboratory Treatment Response (CRP) up to 28 days • Dyspnea up to 28 days • Oxygen saturation without supplemental oxygen, up to 28 days • Oxygen therapy, up to 28 days
Sponsor/ lead institution, country (also country of recruitment if different)	Shahid Beheshti University of Medical Sciences, Iran	King Abdullah International Medical Research Center, Saudi Arabia	Baqiyatallah Medical Sciences University, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see “List of abbreviations” at page 5.

Table 4-33 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir, continued

Trial Identifier/registry ID(s)/contact	Iranean registry of Randomised Trials (IRCT) ID: IRCT20200318046812N1 Contact: Mostafa Ghanee; +98 21 8860 0067; mghaneister@gmail.com	Iranean Registry of Randomised Trials (IRCT) ID: IRCT20200428047228N1 Contact: Mohammad Fathi; +98 21 2351 5366; m.fathi@sbmu.ac.ir	ClinicalTrials.gov ID: NCT04303299 Acronym: previously THDMS-COVID-19; currently FIGHT COVID-19. Contact: Subsai Kongsaengdao; 66818180890; skhongsa@gmail.com
Study design, study phase	Phase 3 Randomized, multicenter open label controlled trial with parallel group design. Block randomization methods using variable block size of four and six stratified by center, using excel.	Phase 3 Double blinded randomized controlled trial with parallel group assignment. Masking of participants, care providers & outcome assessors. Simple randomization using a Random Number Table	Phase 3 Open label eight-arm randomised controlled study with parallel group design. PROBE design - prospective randomised open blinded evaluation). Outcome assessors are masked for allocation status.
Recruitment status	Recruitment completed (last update at registry: 19 Sept. 2020)	Recruitment complete (last update at registry: 16 May 2020)	Recruiting (last update at trial registry 1 Sept. 2020)
Number of Patients, Disease severity*	324 planned; 424 actual Diagnosis of COVID-19 based on either ground glass appearance in chest CT scan or positive RT-PCR test for COVID-19; Requiring hospitalization	50 Not reported	320 Mild to critical COVID-19
Setting (hospital, ambulatory,..)	Hospitalised	Hospitalised	In- and outpatients
Intervention (generic drug name and dosage)	hydroxychloroquine plus favipiravir drug regimen: • Stat dose of eight 200 mg Favipiravir tablets (total 1600 mg) and stat dose of two 200mg Hydroxychloroquine tablets (total 400 mg) followed by Favipiravir 600 mg three times a day for 7 days. This regimen could be continued for 10 days if necessary according to clinical response of the patient. Other supportive and routine care will be the same in both groups.	Favipiravir: • 1600 mg of Favipiravir BID on day 1, 600 mg of Favipiravir BID on day 2-5, and concurrent hydroxychloroquine, 400 mg BID on day 1 and 200 mg hydroxychloroquine bid on day 2-5, and standard treatment (oxygen and, if necessary, antibiotics).	Favipiravir lopinavir /Ritonavir for mod. to severe: • Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Favipiravir 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day in Mild COVID19 In moderate to critically ill COVID19 Darunavir /ritonavir favipiravir chloroquine mod-severe: • Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Favipiravir 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19

Trial Identifier/registry ID(s)/contact	Iranean registry of Randomised Trials (IRCT) ID: IRCT20200318046812N1 Contact: Mostafa Ghanee; +98 21 8860 0067; mghaneister@gmail.com	Iranean Registry of Randomised Trials (IRCT) ID: IRCT20200428047228N1 Contact: Mohammad Fathi; +98 21 2351 5366; m.fathi@sbmu.ac.ir	ClinicalTrials.gov ID: NCT04303299 Acronym: previously THDMS-COVID-19; currently FIGHT COVID-19. Contact: Subsai Kongsaengdao; 66818180890; skhongsa@gmail.com
Comparator (standard care or generic drug name and dosage)	hydroxychloroquine plus kaletra: • Stat dose of two 200 mg Hydroxychloroquine tablets (total 400 mg) followed by Kaletra(Lopinavir/Ritonavir) 200/50 mg two times a day for 7 days. This regimen could be continued for 10 days if necessary according to clinical response of the patient. Other supportive and routine care will be the same in both groups.	Hydroxychloroquine: • Hydroxychloroquine, 400 mg bid on day 1 and 200 mg hydroxychloroquine bid on day 2-5. Increasing the duration of treatment to 10 days, according to the doctor's order. The control group will receive placebo instead of Favipiravir and standard treatment (oxygen and, if necessary, antibiotics).	• Oseltamivir plus Chloroquine in Mild COVID19: Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 800 mg per day In mild COVID19 • Darunavir and Ritonavir plus oseltamivir: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus plus Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 400mg per day in Mild COVID19 • Lopinavir and Ritonavir plus Oseltamivir in mild COVID19: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In mild COVID19 • Lopinavir and Ritonavir Oseltamivir moderate to severe COVID19: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In moderate to critically ill COVID19 • Darunavir /ritonavir oseltamivir chloroquine mod-severe: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19 • Conventional Quarantine: “Patient who unwilling to treatment and willing to quarantine in mild COVID19”
Primary Outcome(s)	• Admission to intensive care unit	• No fever for 3 days • SpO2>93% • CXR observation	• SARS-CoV-2 eradication time up to 24 weeks

Trial Identifier/registry ID(s)/contact	Iranean registry of Randomised Trials (IRCT) ID: IRCT20200318046812N1 Contact: Mostafa Ghanee; +98 21 8860 0067; mghaneister@gmail.com	Iranean Registry of Randomised Trials (IRCT) ID: IRCT20200428047228N1 Contact: Mohammad Fathi; +98 21 2351 5366; m.fathi@sbmu.ac.ir	ClinicalTrials.gov ID: NCT04303299 Acronym: previously THDMS-COVID-19; currently FIGHT COVID-19. Contact: Subsai Kongsaengdao; 66818180890; skhongsa@gmail.com
Sponsor/ lead institution, country (also country of recruitment if different)	Iran university of medical sciences Second sponsor: Bagheiat-allah University of Medical Sciences, Iran	Quality Improvement of Intensive Care Research Center- Shahid Beheshti University, Iran	Rajavithi Hospital; Thailand

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-34 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir, continued

Trial Identifier/registry ID(s)/contact	IRCT20150808023559N20 Contact: Somaieh Matin; +98 45 3325 1410; s.matin@arums.ac.ir
Study design, study phase	Phase 1-2
Recruitment status	Recruitment complete (last update at trial registry at 11 April 2020)
Number of Patients, Disease severity*	N=100 COVID-19 patients requiring hospitalization
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	Favipiravir plus Hydroxychloroquine: • Eight 200 mg Favipiravir tablets (total 1600 mg Nafas farmed Co, Iran) on day 1 followed by Favipiravir 600 mg tid on day 2 to 8 plus Hydroxychloroquine (Iran daroo Co, Iran) 200mg two times per day for 7 days. This regimen could be continued for 10 days if necessary according to clinical response of the patient. Other supportive and routine care will be the same in both groups.
Comparator (standard care or generic drug name and dosage)	Kaletra plus Hydroxychloroquine: • Stat dose of two 200 mg Hydroxychloroquine tablets (total 400 mg) followed by Kaletra (Lopinavir/Ritonavir; Bakhtar bioshimi Co, Iran) 50/200 mg two times a day for 7 days, This regimen could be continued for 10 days if necessary according to clinical response of the patient. Other supportive and routine care will be the same in both groups.
Primary Outcome(s)	Death measured at the time of discharge from the hospital using patient medical records
Sponsor/ lead institution, country (also country of recruitment if different)	Ardabil University of Medical Sciences, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-35 Ongoing trials of combination therapies including Favipiravir and Lopinavir/ritonavir

Trial Identifier/registry ID(s)/contact	EudraCT number: 2020-002106-68 ClinicalTrials.gov ID: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals Contact: FLARE Trial Team UCL CCTU; 020 3108 9840;cctu.flare@ucl.ac.uk
Study design, study phase	Phase 2 Multicenter, randomised, double-blind, 2x2 factorial placebo-controlled trial Masking: triple (participant, care provider, investigator)
Recruitment status	Not yet recruiting (last update at trial registry 5 Aug. 2020*)
Number of Patients, Disease severity*	240 Any. Focus on early manifestations of disease: symptoms compatible with COVID-19 disease within the first 7 days of symptom onset before enrolment or asymptomatic persons who tested positive with SARS-CoV-2 within the last 48 hours before enrolment
Setting (hospital, ambulatory,..)	Not described, likely outpatients
Intervention (generic drug name and dosage)	• Trial arm with combination therapy: • Avigan (Favipiravir) 200 mg daily + Kaletra (Lopinavir/ritonavir) 200/50 mg daily, oral intake Trial arm with single agent: • Avigan (Favipiravir) 200 mg daily Trial arm with single agent: Kaletra (Lopinavir/ritonavir), 200/50 mg daily, oral intake
Comparator (standard care or generic drug name and dosage)	Matched Placebo, oral intake, dosing scheme and mg identical to Avigan and Kaletra schemes.*
Primary Outcome(s)	upper respiratory tract viral load at Day 5 as measured with quantitative polymerase chain reaction (PCR) performed on saliva samples
Sponsor/ lead institution, country (also country of recruitment if different)	University College London Comprehensive Clinical Trial Unit, UK

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5.

Table 4-36 Ongoing trials of combination therapies including Favipiravir and Tocilizumab

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04310228* [16] Chinese Clinical Trial Registry ID: ChiCTR2000030894 Contact: Hong Zhao; 13810765943; zhaohong_pufh@bjmu.edu.cn
Study design, study phase	Phase not described Multicenter three-arm open label randomized controlled trial with parallel group assignment
Recruitment status	Recruiting (last update at trial registry 10 April 2020)
Number of Patients, Disease severity**	150 Not described, cases of respiratory failure and requiring mechanical ventilation were excluded
Setting (hospital, ambulatory,..)	Not described
Intervention (generic drug name and dosage)	Favipiravir group: • 1600 mg BID on day 1; 600mg BID on day 2-7 (maximum). Oral administration. Favipiravir Combined With Tocilizumab group: • Favipiravir: 1600 mg BID on day 1, 600 mg BID on day 2-7 (maximum). Oral administration. Tocilizumab: The first dose is 4 ~ 8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg
Comparator (standard care or generic drug name and dosage)	Tocilizumab group: • the first dose is 4 ~ 8 mg/kg and the recommended dose is 400 mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg.
Primary Outcome(s)	• Clinical cure rate at 3 months (trial registration site) • Cumulative lung lesion remission rate: lung CT examination indicated absorption of lung inflammation (published report)
Sponsor/ lead institution, country (also country of recruitment if different)	Peking University First Hospital, China

* An interim report has been published, outcome data are included in Table 4.4, Table 4.5 and Table 4.6 [16]; **Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Abbreviations: see "List of abbreviations" at page 5.

Table 4-37 Ongoing trials of combination therapies including Favipiravir and other antiviral substances: Umifenovir or Maraviroc

Trial Identifier/registry ID(s)/contact	CTRI/2020/06/025957 Sponsor Protocol Number: GPL/CT/2020/004/III, Version:4.0, Dated:03-Jun-2020	NCT04475991 Acronym: COMVIVIR
Study design, study phase	Two arm open label multicenter randomized controlled trial with parallel group assignment. Use of centralized computer based randomization. Phase 3	Four arm randomized open label controlled trial with parallel group assignment Phase 2
Recruitment status	Open to recruitment (last update at registry on 14 Sept. 2020)	Not yet recruiting (last update at trial registry 9 Feb. 2021)
Number of Patients, Disease severity*	158, moderate COVID-19,	100, Severe non critical COVID-19
Setting (hospital, ambulatory,..)	Hospital	Hospital
Intervention (generic drug name and dosage)	Arm 1 Favipiravir & Umifenovir combined with SOC: • Favipiravir: use of 200 mg tablets for oral use. 3,600 mg (1,800 mg BID) on day 1 + 1,600 mg (800 mg BID) on day 2 to 14 days (maximum) combined with • Umifenovir: use of oral capsules of 800 mg, BID (1,600 mg) • Standard supportive care, not further described	Arm 1 Favipiravir combined with SOC • Favipiravir + Currently used therapy: Favipiravir tablets 200 mg. given orally for a 7 day period. 1600 mg bid on day 1 and 600 mg tid days 2-7 AND Currently used therapy (see description at comparator). Arm 2 Maraviroc+Favipiravir+ Currently used therapy • Maraviroc tablets. 300 mg BID, given orally for a 10 day period AND Favipiravir tablets 200 mg. given orally for the first 7 days. 1600 mg bid on day 1 and 600 mg tid days 2-7 AND Currently used therapy (see description at comparator). Arm 3 Maraviroc + Currently used therapy • Maraviroc tablets. 300 mg bid, given orally for a 10 day period AND Currently used therapy
Comparator (standard care or generic drug name and dosage)	Arm 2 favipiravir combined with standard supportive care • Favipiravir: use of 200 mg tablets for oral use. 3,600 mg (1,800 mg BID) on day 1 + 1,600 mg (800 mg BID) on day 2 to 14 days (maximum) • Standard supportive care, not further described	Arm 4 Currently used therapy for COVID-19 severe non-critical patients • Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present
Primary Outcomes	Time from randomization to clinical cure [Time Frame: Up to 28 days] Details: defined as resolution of baseline clinical signs and symptoms of COVID-19 infection and at least 2 point improvement on WHO Ordinal Scale for Clinical Improvement	Patients free of mechanical ventilation or death [Time Frame: 28 days post start]
Sponsor/ lead institution, country (also country of recruitment if different)	Glenmark Pharmaceuticals Ltd, India Contact: Dr Pawan Singh; Pawan.Singh@glenmarkpharma.com	Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico Contact: Adolfo Pérez-García; +52(55)27892000 Ext. 1151 ; aperezg@hotmail.com

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Abbreviations: CTRI= Clinical Trials Registry-India Identifier; NCT= ClinicalTrials.gov Identifier; SOC=standard of care; BID=twice daily; TID= three times daily.

Table 4-38 Ongoing trials of combination therapies including Favipiravir and other substances: Nafamostat Mesilate or Nitazoxanide

Trial Identifier/registry ID(s)/contact	Japan Registry of Clinical Trials ID: jRCTs031200026 Contact: Kyoji Moriya; +81-3-3815-5411; moriya-tky@umin.org	ClinicalTrials.gov ID: NCT04532931 Other Study ID Numbers: SP-PA-COV-202 Contact: Farouk Chughlay; Telephone: +41 22 555 0355; chughlayf@mmv.org
Study design, study phase	Multicenter, single blinded randomized controlled, comparative trial with parallel group assignment Phase not described	Randomized, adaptive, single center open label controlled trial with parallel group design. Phase 2
Recruitment status	Recruiting (last update at registry: 22 Dec. 2020)	Recruiting (last update at registry: 20 Dec. 2020)
Number of Patients, Disease severity*	160 COVID-19 with pneumonia. Excluded are patients "having less than 93% of oxygen saturation (SpO2) in without the oxygen administration"	250 Mild
Setting (hospital, ambulatory,..)	Likely hospitalised	Outpatients
Intervention (generic drug name and dosage)	Arm 1 Favipiravir + Nafamostat Mesilate • Favipiravir and Nafamostat Mesilate & standard treatment not further specified	All experimental arms also receive standard of care (SOC) as described in the comparator. Arm 1 Artesunate + Amodiaquine: • SOC plus artesunate-amodiaquine (ASAQ) - 2 tablets (200/540 mg artesunate/amodiaquine) daily for 3 days Arm 2 Pyronaridine + Artesunate: • SOC plus pyronaridine-artesunate (PA) Weight 45 to <65 kg: 3 tablets (540/180 mg pyronaridine/artesunate) daily for 3 days Weight ≥65 kg: 4 tablets (720/240 mg pyronaridine/artesunate) daily for 3 days Arm 3 Favipiravir + Nitazoxanide • SOC plus favipiravir plus nitazoxanide (FPV-NTZ) Favipiravir: 1600 mg 12-hourly for 1 day then 600 mg 12-hourly for 6 days Nitazoxanide: 2 tablets (1000 mg) 12-hourly for 7 days Arm 4 Sofosbuvir + Daclatasvir • SOC plus sofosbuvir/daclatasvir (SOF/DCV) 1 tablet (400 mg/60 mg sofosbuvir/daclatasvir) daily for 7 days
Comparator (standard care or generic drug name and dosage)	Arm 2 Favipiravir & standard treatment: • not further specified	Arm 5 SOC • paracetamol, 2 tablets (1000 mg) to be taken 6-hourly as needed
Primary Outcome(s)	The primary outcome listed at the trial register changed on 22 Dec. 2020, in the recruitment phase. Current: Change in patient condition on a 10-point scale from baseline to day 7 Previous the following were listed: • Time to alleviation of body temperature • Time to alleviation of SpO2	Incidence of SARS-CoV-2 clearance [Time Frame: Day 7]: proportion of participants with a negative nasal swab

	• Time to alleviation of chest image findings • time to SARS-CoV-2 PCR turn negative	
Sponsor/ lead institution, country (also country of recruitment if different)	Not reported, likely the University of Tokyo, Japan	Shin Poong Pharmaceutical Co. Ltd. Recruitment in South Africa, Johannesburg

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see list of abbreviations at page 5

Table 4-39 Ongoing trial of combination therapies including Favipiravir and other substances: antibiotics

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov ID: NCT04613271 Other Study ID Numbers: FVR Contact: Dr. Armedy Ronny Hasugiana, M. Biomed; +62 21 42879189; medyrh@gmail.com	JPRN-jRCTs051200049 Acronym: COVID-DMC Contact: Iwahori Kota; +81-6-6879-8413; iwahori@climm.med.osaka-u.ac.jp
Study design, study phase	Multicenter two-arm open label randomized controlled trial with parallel group assignment Phase 3	Multicenter three-arm open label randomized controlled trial with parallel group assignment Phase not reported
Recruitment status	Suspended, study halted prematurely but potentially will resume, the protocol will be amended (last update at registry on 27 Jan. 2021)	Recruiting (last update at registry on 29 Oct. 2020)
Number of Patients, Disease severity*	210 mild-moderate COVID-19 patients	30 COVID-19 with pneumonia patients not needing continuous (24h) oxygen inhalation
Setting (hospital, ambulatory,..)	Hospital	Hospital
Intervention (generic drug name and dosage)	Favipiravir: 1600 mg twice a day at day 1 and 600 mg twice a day at day 7-14 + Azithromycin 500 mg once a day for 5 days.	Arm 1: Demethylchlortetracycline 150mg/day once daily for 14 days plus Favipiravir for 10 days (max 14 days) Arm 2: Demethylchlortetracycline 150 mg bid (total 300mg/day) for 14 days plus Favipiravir for 10 days (max 14 days)
Comparator (standard care or generic drug name and dosage)	Azithromycin 500 mg once a day for 5 days.	Arm 3: Favipiravir only for 10 days (max 14 days)
Primary Outcome(s)	Clinical improvement measured by no sign & symptom for 3 days and RT PCR negative	The change rate of CD8+ T cells between before and 7 days after the administration of the study drug (outcomes relevant to this report are listed as secondary outcomes in the trial registration).
Sponsor/ lead institution, country (also country of recruitment if different)	Ina-Respond, Indonesia	SHIONOGI & CO., LTD.; Japan

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5

Table 4-40 Ongoing trial of combination therapies including Favipiravir and other substances: Interferon beta-1a

Trial Identifier/registry ID(s)/contact	IRCT20200506047323N3 [32] Contact: Mohammad Fathalipour; +98 76 3371 0406; m.fathalipour@hums.ac.ir
Study design, study phase	Multicenter two-arm open label randomized controlled trial with parallel group assignment Use of block randomization with block size of 6. Allocation sequence and concealment codes will be generated using www.sealedenvelope.com. The closed envelope method will be used to hide the allocation sequence. Phase 3
Recruitment status	Recruitment completed (last update at registry on 22 July 2020)
Number of Patients, Disease severity*	60 COVID-19 not further specified
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	Favipiravir plus Interferon beta-1a: • favipiravir (Zhejiang Hisun, China) 1600 mg twice a day on day 1, 600 mg twice a day on day 2 to 5, plus five doses of 44 mcg Interferon beta-1a (CinnaGen, Iran) every other day. Other supportive and routine care will be the same in both groups.
Comparator (standard care or generic drug name and dosage)	Lopinavir/Ritonavir and Interferon beta-1a: • Lopinavir/Ritonavir (Heterd company, India) 200/50 mg twice a day on day 1 t 7, plus five doses of 44 mcg Interferon beta-1a every other day. Other supportive and routine care will be the same in both groups.
Primary Outcome(s)	• viral load • fever • Oxygen saturation
Sponsor/ lead institution, country (also country of recruitment if different)	Bandare-abbas University of Medical Sciences, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5

Table 4-41 Ongoing trial of combination therapies including Favipiravir and other substances: Camostat mesilate and ciclesonide

Trial Identifier/registry ID(s)/contact	JPRN-jRCTs031200196 Contact: Tsushima Kenji: +81-476-35-5600; ktsushima@iuhw.ac.jp
Study design, study phase	Multicenter two-arm open label randomized controlled trial with parallel group assignment Phase not described
Recruitment status	Recruiting (last update at registry on 6 Jan. 2021)
Number of Patients, Disease severity*	100 COVID-19 with pneumonia patients
Setting (hospital, ambulatory,..)	Hospital

Intervention (generic drug name and dosage)	Combination therapy with favipiravir, camostat mesilate and inhaled ciclesonide for 10 days. Details on dosing not reported.
Comparator (standard care or generic drug name and dosage)	Active control, not further specified
Primary Outcome(s)	Length of hospital stay
Sponsor/ lead institution, country (also country of recruitment if different)	Japan Agency for Medical Research and Development (AMED), Japan

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5

Table 4-42 Ongoing trial of combination therapies including Favipiravir and other substances: Montelukast

Trial Identifier/registry ID(s)/contact	NCT04718285 Contact: Prof. Serdar Durdagi; +90-216-579-8217; serdar.durdagi@med.bau.edu.tr
Study design, study phase	Multicenter three-arm open label randomized controlled trial with parallel group assignment Phase 2
Recruitment status	Not yet recruiting (last update at registry on 27 Jan. 2021)
Number of Patients, Disease severity*	N=380
Setting (hospital, ambulatory,..)	outpatients
Intervention (generic drug name and dosage)	Trial arm Montelukast: 6x10 mg oral montelukast daily for 14 days Trial arm Montelukast plus Favipiravir: 200 mg oral favicovir for 5 days in a regimen of 2x1600 mg (oral) loading dose on day-1 (eight tablets in the morning and eight tablets in the evening) followed by 2x600 mg maintenance dose (three tablets in the morning and three tablets in the evening) on day-2 to day-5 and 6x10 mg oral montelukast daily for 14 days, concurrently.
Comparator (standard care or generic drug name and dosage)	Trial arm: Favipiravir: 200 mg oral favicovir for 5 days in a regimen of 2x1600 mg (oral) loading dose on day-1 (eight tablets in the morning and eight tablets in the evening) followed by 2x600 mg maintenance dose (three tablets in the morning and three tablets in the evening) on day-2 to day-5. Favipiravir is used as Standard Treatment.
Primary Outcome(s)	Hospitalized patient rates: The number of hospitalized patients up to 15 days
Sponsor/ lead institution, country (also country of recruitment if different)	Bahçeşehir University, Turkey

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: see "List of abbreviations" at page 5

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	05/02/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	05/02/2021
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	05/02/2021
Google	scholar.google.com & google.com	Performed on all identified ongoing studies: google and google scholar search using trial registry ID or acronym as search term (0 newly identified RCT with outcome data)	15/01/'21
PubMed	pubmed.ncbi.nlm.nih.gov	Performed on all identified ongoing studies: PubMed search using trial registry ID or acronym as search terms (3 newly identified protocols to already identified RCT)	15/01/'21
Citation screening	-	Citation screening of all systematic reviews evaluating favipiravir, identified in NIH LitCovid and NIPH (n=17 systematic reviews)	10/09/'20

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies. Before that date, SNHTA was responsible.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [33, 34]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in table 6.2 for this version of the report. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated a long with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

Table 6-2 depicts both the search strategy executed by NIPHNO and the search strategy by SNHTA for this and previous versions of the report.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits
Search strategy as executed by NIPHNO for the current version of the report				4564
Embase 1974 to 2021 **Ovid MEDLINE(R) ALL 1946 to 2021**		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE]	From 1/9/2020 until 3/2/2021 Covering publication dates 01. September 2020	

		2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or REGN-COV-2/ or bamlanivimab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (REGN-CoV-2 or REGN-CoV2 or antibody cocktail or ((casirivimab or REGN-10933 or REGN10933) and (imdevimab or REGN-10987 or REGN10987))) or (bamlanivimab		

Database	URL	Search terms / Search modality	Date of search	Hits
		or LY-CoV555 or LYCoV555 or LY-3819253 or LY3819253) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 OR MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE] 7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dc. use oemezd [time limits in Embase] 8 (1 and (3 or 5) and 6) use medall 9 (2 and (4 or 5) and 7) use oemezd		
Search by SNHTA performed for version 7 of the report				
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at “condition or disease”: • covid-19 Terms used at “other terms”: • favipiravir Synonyms for COVID-19 and favipiravir are automatically searched	15/ 02/’21	48 3 new
ICTRP COVID-19 collection accessed through search platform of clincaltrials.gov	https://clinicaltrials.gov/ct2/who_table	Basic search mode Terms used: favipiravir	15/02/’21	45 0 new
Search strategy as executed by NIPHNO for version 6 of the report				
FHI Live COVID-19 Evidence Map	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab	

Database	URL	Search terms / Search modality	Date of search	Hits
OVID Medline	Imported from EPPI Centre	1. exp Coronavirus/ 2. exp Coronavirus Infections/ 3. (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4. (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) 5. 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6. ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8. COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab	
		9. ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10. or/6-9 11. 5 or 10		
OVID EMBASE		1. exp Coronavirus Infections/ 2. exp coronavirinae/ 3. (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4. or/1-3 5. 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6. ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8. 6 or 7 9. 5 or 8	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab	

Database	URL	Search terms / Search modality	Date of search	Hits
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR covid-19 OR "covid 2019" OR ((novel OR new OR nouveau) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	1/12/2020 until 04/01/2021 And from 1/09/2020 until 04/01/2021 for the new compounds Vitamin D, Aspirin and Mavrilimumab	
Search Strategy as executed by SNHTA for version 6 of the report				
ICTRP COVID-19 collection accessed through search platform of clincaltrials.gov	https://clinicaltrials.gov/ct2/who_table	Basic search mode Terms used: favipiravir	15/01/'21	45 3 new (ongoing)
Search by NIPHNO performed for version 5 of this report				
FHI Live COVID-19 Evidence Map	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	26/10/'20 until 30/11/'20 And from 1/09/'20 until 30/11/'20 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir	317
Search by NIPHNO performed for version 4 of this report				
FHI Live COVID-19 Evidence Map	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	27/09/'20 until 25/10/'20	378
Search by NIPHNO performed for version 3 of this report				
FHI Live COVID-19 Evidence Map	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	24/08/'20& 27/09/'20	460
Search Strategy as executed by SNHTA for version 1 and 2 of this report				
NIH LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/	Favipiravir* OR avigan or Favipiravirum or Abigan or Avifavir or Areplivir or FabiFlu or Favipira	10/09/'20	124
NIPH	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Seaching "Interventions to treat the infected patient" Ticking "Flavipiravir", "Any population"	10/09/'20	14
Citation screening	-	Citation screening of all systematic reviews evaluating favipiravir, identified in NIH LitCovid and NIPH (n=17 systematic reviews)	10/09/'20	1
Google	scholar.google.com & google.com	Performed on all identified ongoing studies: google and google scholar search using trial registry ID or acronym as search term	15/09/'20	0

***** all hits retrieved with search term favipiravir

6.3 Search strategy to identify ongoing studies

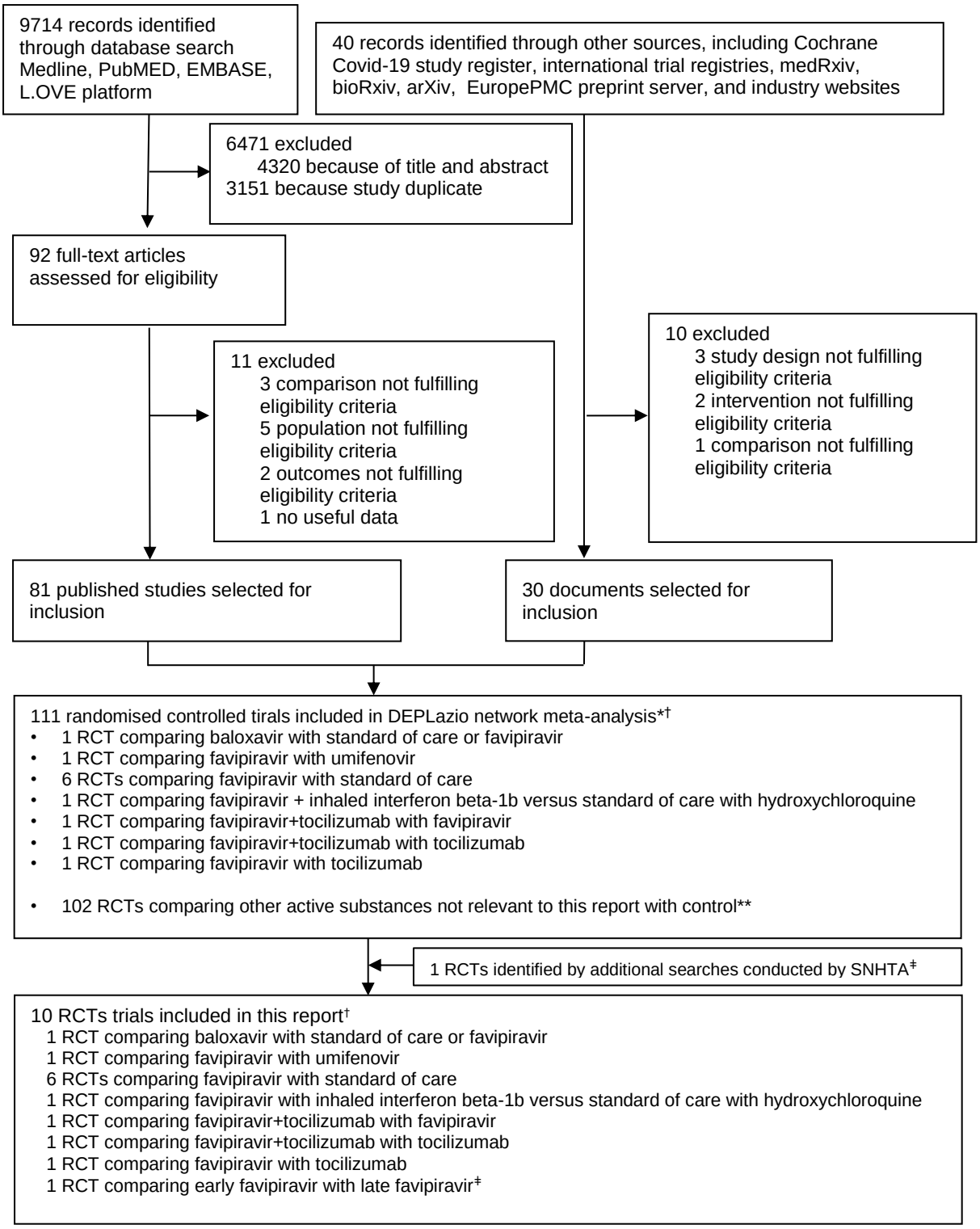
SNHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and favipiravir are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

Database	URL	Search terms / Search modality	Date of search	Hits / newly included
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at "condition or disease": • covid-19 Terms used at "other terms": • favipiravir Synonyms for COVID-19 and favipiravir are automatically searched	15/ 02/'21	48 3 new
ICTRP COVID-19 collection accessed through search platform of clincaltrials.gov	https://clinicaltrials.gov/ct2/who_table	Basic search mode Terms used: favipiravir	15/02/'21	45 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and Favipiravir • covid-19 and avigan • covid-19 and T-705 • covid-19 and Favilavir • covid-19 and Fapilavir • covid-19 and Favipiravirum • covid-19 and Abigan • covid-19 and Avifavir • covid-19 and Areplivir • covid-19 and Fabi Flu • covid-19 and Favipira • covid-19 and favicovir The same intervention terms were combined with the term «SARS»	15/02/'21	Overall: 1 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • see ISRCTN, the same search terms were used here	15/02/'21	8 0 new
Cochrane COVID-19 Study register	https://covid-19.cochrane.org/	Filtered by favipiravir	15/02/2021	39 4 new
Citation screening	-	Citation screening of all systematic reviews evaluating favipiravir, identified in NIH LitCovid and NIPH (n = 17 systematic reviews), see Appendix Table 6-1	14/10/'20	11

***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.1 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

RCT = randomised controlled trial
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914; the identified trials are all considered in the summary of findings tables in this report.
† Some trials contribute with two or more comparisons
‡ one identified trial with outcome data was identified by screening of citation lists of recent systematic reviews and by searching PubMed and Google Scholar, using trial registry identification numbers and trial acronyms, and by screening included RCTs at covid-nma.com. This trial was excluded by DePlazio but is described in this report;

Table 6-4 Additional findings for published RCTs included in summary of findings tables, related to effectiveness and safety of Favipiravir versus standard care

Patient or population: COVID-19 infection
Setting: Hospital inpatients and outpatients
Intervention: Favipiravir & standard care[a]
Comparison: Standard care[a]

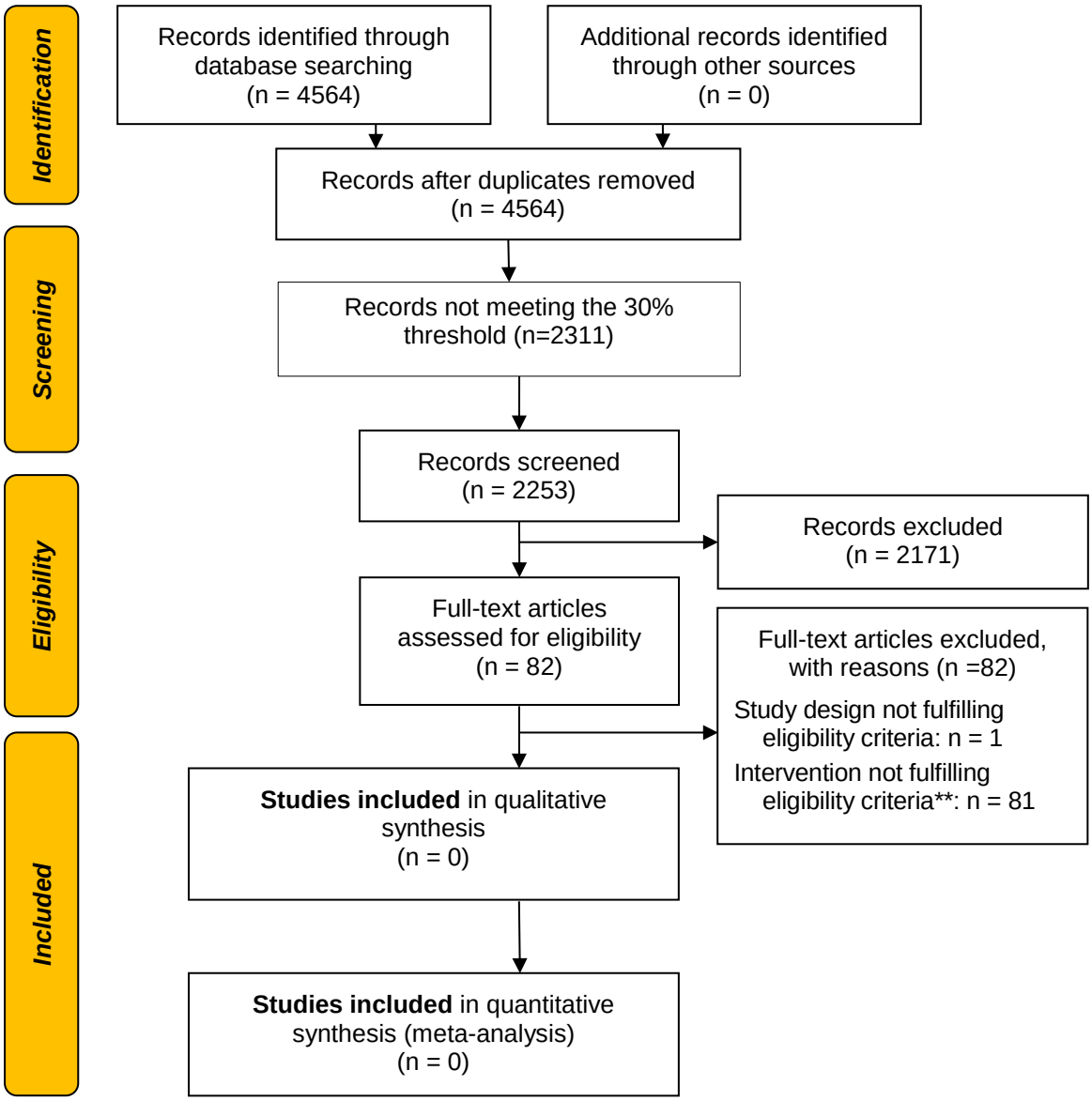
Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (RCTs)	Certainty of evidence
	Risk with standard care	Risk with Favipiravir				
Improvement in lung disease on CT, day 7 up to 14 days	307 per 1000	336 per 1000 (285 to 445)	RR 1.16 (0.93 to 1.45)	49 more per 1000 (from 21 fewer to 138 more)	88 (3[b,c]) [8, 9, 11]	low[d,e,f]
clinical improvement D7 In- & outpatients	221 per 1000	349 per 1000 (254 to 477)	RR 1.58 (1.15 to 2.16)[g]	128 more per 1000 (from 33 more to 256 more)	379 (3) [10, 11, 13]	low[d,h]
clinical improvement D14-D28 In- & outpatients	895 per 1000	895 per 1000 (868 to 931)	RR 1.00 (0.97 to 1.04) [g]	0 more per 1000 (from 27 fewer to 36 more)	379 (4) [9-12]	low[d,h]
incidence viral negative conversion D3 In- & outpatients	455 per 1000	555 per 1000 (450 to 682)	RR 1.22 (0.99 to 1.50) [g]	100 more per 1000 (from 5 fewer to 227 more)	318 (3) [10-12]	low[i,j]
incidence viral negative conversion D7 In- & outpatients	688 per 1000	750 per 1000 (653 to 867)	RR 1.09 (0.95 to 1.26) [g]	62 more per 1000 (from 34 fewer to 179 more)	677 (6)[8-13]	very low[i,j,k]
Invasive ventilation In- & outpatients	0 per 1000	0 per 1000 (0 to 0)	RR 1.51 (0.06 to 36.56) [l]	0 fewer per 1000 (0 fewer to 0 fewer)	368 (1) [11, 13]	very low[e,m]
who progression score level 6 or above D7	100 per 1000	300 per 1000 (37 to 1000)	RR 3.00 (0.37 to 24.17) [g]	200 more per 1000 (from 63 fewer to 1000 more)	20 (1) [10]	very low[n,o,p]
who progression score level 6 or above D14-28 *Inpatients*	None of the patient in either trial arm had level 6 or above - [e]		not estimable	-	220 (1) [10, 13]	very low[n,q]
who progression score level 7 or above D7 *Inpatients*	None of the patient in either trial arm had level 7 or above - [e]		not estimable	-	20 (1) [10]	very low[o,q,r]
who progression score level 7 or above D14-28 *Inpatients*	None of the patient in either trial arm had level 7 or above [e]		not estimable	-	220 (1) [10, 13]	very low[q,r]
Length of stay in hospital	-	-	HR 1.41 (0.97 to 2.03)	-	148 (1) [12]	low[e,s]
Number of patients with adverse events	288 per 1000	426 per 1000 (251 to 732)	RR 1.48 (0.87 to 2.54)	138 more per 1.000	571 (4[l]) [9, 11-13]	very low[n,t,u]

In- & outpatients				(from 37 fewer to 444 more)		
Withdrawals due to AEs[l] *In- & outpatients*	6 per 1000	7 per 1000 (1 to 71)	RR 1.02 (0.09 to 10.99)[l]	0 fewer per 1000 (from 6 fewer to 64 more)	363 (2) [11, 13]	very low[s,v]
Time to clinical improvement *In- & outpatients*	-	-	HR 1.52 (1.17 to 1.96)[g]		299 (2) [11, 12]	low [w,x]

Source: Outcome data from the department of Epidemiology Lazio Regional Health Service (DEPLazio) in Italy unless otherwise declared [22], GRADE-assessment adapted from COVID-nma.com or by SNHTA; descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk. HR=hazard ratio
Evaluation of the quality of the tests according to the GRADE Working Group
High Quality: We are very confident that the real effect is close to that of the estimated effect
Moderate Quality: We are moderately confident in the effect estimation: the real effect may be close to the estimated effect, but there is a possibility that it is substantially different
Low Quality: Our confidence in the effect estimation is limited: the real effect may be substantially different from the estimated effect
Very Low Quality : We have very little confidence in estimating the effect: the actual effect is likely to be substantially different from the estimated one.

Explanations

a. In the study of Lou both groups receive standard treatment involving the administration of Lopinavir / Ritonavir or Darunavir / Cobicistat and Umifenovir, in combination with interferon α, in the Ivashchenko study standard treatment consisted of hydroxychloroquine or chloroquine in 15/20 (75.0%) of patients, lopinavir/ritonavir in 1/20 (5%). Four (20%) patients did not receive etiotropic treatment. In the Ivashchenko study, the concomitant therapy of COVID-19 in all groups included antibiotics, anticoagulants and/or immunosuppressants, as well as symptomatic treatment. in Dabbous 2020, the control group received hydroxychloroquine + oseltamivir which was considered as standard of care in Egypt. In Udwadia, standard treatment included antipyretics, cough suppressants, antibiotics, and vitamins [12]. In Ruzthentsova, standard care was according to the Russian Ministry of Health and the standards of the trial site, including umifenovir + intranasal interferon alpha-2b, or hydroxychloroquine, antipyretics, antibiotics, anticoagulants, vasoconstrictor drugs [11].
b. In Dabbous 2020, subgroup data from persons with chest CT confirmed defects at baseline is used (outcome data added by SNHTA).
c. In Ivashchenko 2020, trial arms of the FVP 1600 mg and FVP 1200 mg were combined before pooling across studies.
d. Downgraded by one level for rob: some concerns regarding adequate randomization, deviation from intended intervention, outcome measurement and selection of reported results
e. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm
f. Outcome data and GRADE assessment by SNHTA. The outcome data in the trial Balykova 2020 were not included in the meta-analyses, as the exact numbers were unclear.
g. Outcome data from covid-nma.com
h. Downgraded by one level for imprecision: due to low number of events and/or participants
i. Downgraded by one level for rob: some concerns regarding adequate randomization, deviation from intended intervention and selection of reported results
j. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect
k. Downgraded by one level for inconsistency: I^2=50%
l. Outcome added by SNHTA
m. Downgraded by one level for rob: some concerns regarding deviation from intended intervention
n. Downgraded by one level for rob: some concerns regarding adequate randomization, deviation from intended intervention and outcome measurement
o. Downgraded by one level for indirectness: single study from a single institution, therefore results in this population might not be generalizable to other settings
p. Downgraded by two levels for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
q. Downgraded by two levels for imprecision: no events in both groups and low number of participants
r. Downgraded by one level for rob: some concerns regarding adequate randomization and deviation from intended intervention
s. Downgraded by one level for rob: some concerns regarding deviation from intended intervention and outcome measurement
t. Downgraded by one level for inconsistency: I^2 =76%, calculation by SNHTA
u. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for no effect and the possibility for harm
v. Downgraded by one level for imprecision: due to very wide confidence interval consistent with the possibility for no effect and the possibility for harm
w. Downgraded by one level for rob: some concerns regarding deviation from intended intervention, outcome measurement and selection of reported results
x. Downgraded by one level for indirectness: the definition for clinical improvement differed in the two trials. Clinical improvement was time to hospital discharge in Udwadia 2020 [12] and according to the WHO 8-Category Ordinal Scale in Ruzthentsova 2020 [11]. The pooled estimate favours the use of favipiravir. Balykova 2020 outcome data was not included: Median (IQR): 8 days (6 to 10) in the FV group; Median (IQR): 12 days (7 to 12) in the SoC group; Between group difference of 4 days, P<0.0001)



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
* Hits from searches executed by NIPHNO in the period 1 September to 3 February 2021
** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews
ł Two completed controlled clinical trials, one single arm study and three ongoing observational studies identified by searches executed by SNHTA in earlier versions of this report are not listed here (Table 6-2).