EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

FAVIPIRAVIR FOR THE TREATMENT OF COVID-19

Project ID: RCR11
Monitoring Report

Version 4.0, November 2020

Template version October 2020

This Rolling Collaborative Review Living Document is part of the project / joint action ‘724130 / EUnetHTA JA3’ which has received funding from the European Union’s Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**17/08/2020**	First version
V 1.1	**10/09/2020**	Literature searches, Literature screening, Data extraction
V 1.2	**15/09/2020**	Data extraction and analysis complete
V 1.3	**17/09/2020**	Check of data extraction and analysis
V 2.0	**17/09/2020**	Second version
V 3.0	**14/10/2020**	Third version
V 4.0	**17/11/2020**	Fourth version

Major changes from previous version

Chapter, page no.	Major changes from version 3.0
Methods, 9	The description of the selection methods for observational studies is expanded: • Studies enrolling less than 50 patients are excluded from the report
Summary, 13-14 **Table 4-10, 29** **Table** 4-22**, 49** **Table 6.4 – 6.5, 60** **Table 4-1, 15**	The pool of included studies has changed. The following were added: • three ongoing 2-arm phase-3 RCTs (ClinicalTrials.gov Identifier: NCT04613271 (210 participants), NCT04600895 (826 participants) and NCT04600999 (150 patients). • One 2-arm trial (89 participants) not previously identified has a journal pre-proof [1] • One trial previously listed as ongoing has published outcome data (ClinicalTrials.gov Identifier: NCT04542694) • Outcome data of 1 RCT was added to the Summary of Findings table. The following was deleted • A selection criteria for observational studies was added, restricting inclusion to studies enrolling at least 50 patients. As a consequence, two small observational studies were excluded from the report (Yamamura 2020[2]; Doi 2020[3]).
Table 4-5, 21 to Table 4-22, 47	Actual status of all ongoing trials listed in Tables 4 are verified and updated when indicated

Disclaimer

The content of this “Rolling Collaborative Review” (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA’s participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Rolling Collaborative Review team

Author(s)	Swiss Network for Health Technology Assessment (SNHTA), Switzerland
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

Further contributors

Project Management	
Zorginstituut Nederland (ZIN), Netherlands	Coordination between involved parties throughout the assessment
Austrian Institute for Health Technology Assessment (AIHTA), Austria	Coordination of RCR

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).

Copyright

How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR11) Authoring Team. Favipiravir for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 64 pages. Report No.: RCR11. Available from: https //www.eunethta.eu.

Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

TABLE OF CONTENTS

DOCUMENT HISTORY AND CONTRIBUTORS **2**
TABLE OF CONTENTS **4**
LIST OF TABLES AND FIGURES **4**
1 OBJECTIVE **7**
2 METHODS **7**
2.1 SCOPE *7*
2.2 SOURCES OF INFORMATION *9*
3 ABOUT THE TREATMENT **11**
3.1 MODE OF ACTION *11*
3.2 REGULATORY STATUS *11*
3.3 LEVEL OF EVIDENCE *11*
4 SUMMARY **13**
4.1 EFFECTIVENESS AND SAFETY EVIDENCE FROM RCTS *13*
4.2 SAFETY EVIDENCE FROM OBSERVATIONAL STUDIES *13*
4.3 ONGOING STUDIES *13*
4.4 SCIENTIFIC CONCLUSION ABOUT STATUS OF EVIDENCE GENERATION *14*
5 REFERENCES **51**
6 APPENDIX **53**
6.1 SEARCH STRATEGY TO IDENTIFY RANDOMISED CONTROLLED TRIALS *53*
6.2 SEARCH STRATEGY TO IDENTIFY OBSERVATIONAL STUDIES *56*
6.3 SEARCH STRATEGY TO IDENTIFY ONGOING STUDIES *58*
6.1 FLOW DIAGRAMS *59*

LIST OF TABLES AND FIGURES

Table 2-1 Scope of the RCR 7
Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Favipiravir 15
Table 4-2. Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir 17
Table 4-3 Summary of safety from observational studies (AE and SAE) of Favipiravir 18
Table 4-4 Summary of safety from observational studies (AE and SAE) of Favipiravir 20
Table 4-5. Ongoing phase 3 trials of single agents: Favipiravir 21
Table 4-6 Ongoing phase 3 trials of single agents: Favipiravir, continued 22
Table 4-7 Ongoing phase 3 trials of single agents: Favipiravir, continued 24
Table 4-8 Ongoing phase 3 trials of single agents: Favipiravir, continued 25
Table 4-9 Ongoing phase 3 trials of single agents: Favipiravir, continued 27
Table 4-10 Ongoing phase 3 trials of single agents: Favipiravir, continued 29
Table 4-11. Ongoing phase 2 trials of single agents: Favipiravir, continued 30
Table 4-12 Ongoing phase 2 trials of single agents: Favipiravir, continued 31
Table 4-13 Ongoing phase 2 trials of single agents: Favipiravir, continued 33
Table 4-14 Ongoing phase 2 trials of single agents: Favipiravir, continued 34
Table 4-15 Ongoing phase 2 trials of single agents: Favipiravir, continued 36
Table 4-16 Ongoing phase 2 trials of single agents: Favipiravir, continued 37
Table 4-17 Ongoing phase 2 trials of single agents: Favipiravir, continued 39
Table 4-18 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir 40
Table 4-19 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir, continued 42

Table 4-20 Ongoing trials of combination therapies including Favipiravir and Lopinavir/ritonavir 45
Table 4-21 Ongoing trials of combination therapies including Favipiravir and Tocilizumab 46
Table 4-22 Ongoing trials of combination therapies including Favipiravir and other antiviral substances: Umifenovir or Maraviroc 47
Table 4-23 Ongoing trials of combination therapies including Favipiravir and other substances: Nafamostat Mesilate or Nitazoxanide 48
Table 4-24 Ongoing trial of combination therapies including Favipiravir and other substances: Azithromycin 49
Table 6-1 Search strategy to identify randomised controlled studies 54
Table 6-2 Search strategy to identify observational studies 56
Table 6-3 Search strategy to identify ongoing studies 58
Table 6-4 Summary of effectiveness and safety from recently identified RCTs of Favipiravir not yet included in summary of findings tables 60
Table 6-5 Summary of effectiveness and safety from recently identified RCTs of Favipiravir not yet included in summary of findings tables 61

Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs 59
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies 63
Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies 64

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
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
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/services/covid-19/) 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:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- 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 [4].

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 [5]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [6].

- 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 using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/

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, registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data, study population of less than 50 participants

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 [7].

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/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of SNHTA is searching and extracting the data for the eligible studies. The process of study selection is depicted in a flow diagram Appendix Figure 6-3. 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 [8].

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 [9, 10].

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, Appendix Figure 6-3).

Two RCTs have been published evaluating favipiravir in Chinese population [11, 12]. One small 3-arm controlled trial randomized 30 hospitalized patients in a 1:1:1 ratio into a baloxavir marboxil group, a favipiravir group, and a control group [12]. 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. A larger RCT compared favipiravir with Umifenovir (arbidol)[11]. 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 report to an additional phase 2/3 3-arm RCT conducted in Russia was included in the Summary of Finding table (Table 4-1, [13]. 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. Methodologic features of these trials are addressed in Table 4-1 and Table 4-2.

In this update, we added outcome data from one trial to the summary of finding table [14]. Trial descriptions were extracted from a report posted on a preprint server, related to the clinicaltrials.gov identifier NCT04349241. The trial was conducted in Egypt and included patients with mild to moderate COVID-19. 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. in Outcome data of this trial may be considered for inclusion in the next update of this report. 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.

We identified additional trials, which will be considered for inclusion in the Summary of Finding tables in the next version of this update. The study with identifier NCT04542694 has posted study results and the statistical analyses plan on the clinicaltrials.gov website. This two-arm randomised open label trial was conducted in Russia and 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. An interim analyses to another RCT was identified, of which no trial registration was found [1]. 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. The RCT with Japan Register of Clinical Trials (JRCT) identifier JPRN-jRCTs041190120, evaluating 89 asymptomatic and mildly ill patients with SARS-CoV2 infection, has now been published in a peer reviewed journal [15]. In addition, summary outcome data has been uploaded to the registration site [16]. This multicenter, open-label, randomized clinical trial evaluated immediate treatment with favipiravir (avigan) on day 1 with a delayed scheme on day 6. The primary endpoint was viral clearance by day 6.

Appendix Figure 6-2 show the selection process for observational studies, resulting in the inclusion of three studies [17-19]. No additional study was identified in this update. One large prospective uncontrolled observational study explicitly reported to evaluate avigan [19]. This multicentre study was conducted in Japan and enrolled 2158 hospitalised patients with mainly mild to moderate Covid-19. 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. 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. Table 4-3 and Table 4-4 describe the Japanese and two additional non-randomised observational studies that reported safety outcomes for Favipiravir of any brandname [17, 18]. One study had a 3-arm comparative design evaluating favipiravir with hydroxychloroquine (HQ) with or without azithromycin (AZ). The third study had a controlled before-after design comparing favipiravir with Lopinavir/ritonavir. The dose schedule of favipiravir provided was similar across the observational studies.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Favipiravir versus standard care

Three RCTs contributed to the estimates presented in the Summary of Findings Table. The certainty of the evidence was very low for each of the outcomes listed in the Table. The three RCTs were too small to measure effects on all-cause mortality. In the Chinese trial, no death occurred in either trial arm during the relative short follow-up duration. The Russian trial reported two death in the 1600/600 mg group, but incompletely described outcome data across the three groups. The Egyptian trial reported one death in the hydroxychloroquine plus oseltamivir control arm due to acute heart failure resulting from myocarditis at day 8.

Due to the very low certainty of the evidence for the comparison favipiravir compared to standard care, we are unsure whether favipiravir may lead to fewer patient with viral clearance, may increase the number of patients with respiratory failure and respiratory distress syndrome, may decrease the number of death, may decrease the number of patients discharged at day 15, may improve lung disease as measured with CT, may increase the number of patients with serious adverse events and may increase the number of patients with adverse events. The current evidence base does not 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.

The outcome data from the Russian trial (NCT04542694) and the trial with Japan Register of Clinical Trials (JRCT) identifier JPRN-jRCTs041190120 will be considered in the Summary of Findings table once the full report has been published. The trial conducted in Oman will be included in the next update of this review. For completeness, we describe the outcome data in the appendix (Table 6-4 and Table 6-5) without considering the certainty of the evidence as latter can be only assessed once the trial report is published.

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 [11]. When compared to umifenovir, favipiravir may increase the number patient with adverse events, but the evidence is very uncertain. 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.

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%) [19]. 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 4-5 to Table 4-21 describe ongoing trials for favipiravir of any brandname.
In this update, we added descriptions to 3 ongoing 2-arm RCTs evaluating favipiravir in COVID-19 patients: ClinicalTrials.gov Identifier: NCT04613271 (210 participants), NCT04600895 (826 participants) and NCT04600999 (150 patients). Overall, 45 ongoing randomised controlled studies are included, of

which 13 evaluate favipiravir in combination with another pharmacotherapy. The remainder evaluate favipiravir as single agent. For several of the identified studies, the brandname was not reported. The trial registration NCT04434248 related to the interim report of the Ivashchenko trial [13] is included in Table 4-12.

4.4 Scientific conclusion about status of evidence generation

The current evidence base does not 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

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

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (RCTs)	Certainty of evidence	Comments
	Risk with standard care	Risk with favipiravir				
SARS-CoV-2 clearance up to 14 days	688 per 1000	646 per 1000 (543 to 756)	RR 0.94 (0.79 to 1.10)	159 (3[a]) [12-14]	very low[b,c]	41 fewer per 1.000 (from 144 fewer to 69 more)
Number of patients with respiratory failure and respiratory distress syndrome	400 per 1000	444 per 1000 (156 to 1000)	RR 1.11 (0.39 to 3.19)	19 (1) [12]	very low[d,e]	44 more per 1.000 (from 244 fewer to 876 more)
All-cause mortality	13 per 1000	4 per 1000 (0 to100)	RR 0.33 (0.01 to 7.99)	159 (3[a]) [12-14]	very low[b,f]	8 fewer per 1000 (from 12 fewer to 87 more). No death occurred during the study period in Lou et al[12].
Number of patients discharged at day 15	850 per 1000	646 per 1000 (451 to 944)	RR 0.76 (0.53 to 1.11)	40 (1[g]) [13]	very low[h,i]	204 fewer per 1.000 (from 399 fewer to 94 more)
Improvement in lung disease on CT up to 14 days	688 per 1000	798 per 1000 (619 to 1000)	RR 1.16 (0.90 to 1.48)	62 (2[g,j]) [13, 14]	very low[h,i]	110 more per 1000 (from 69 fewer to 330 more)
Number of patients with serious adverse events	400 per 1000	444 per 1000 (156 to 1000)	RR 1.11 (0.39 to 3.19)	19 (1) [13]	very low[d,i]	44 more per 1000 (from 244 fewer to 876 more)
Number of patients with adverse events	250 per 1000	500 per 1000 208 to 1000	RR 2.00 (0.83 to 4.81)	40 (1[g]) [13]	very low[h,i]	250 more per 1000 (from 43 fewer to 952 more)

Source: publication by Lou et al, 2020 [20], related to Chinese Clinical Trial Registry ID: ChiCTR2000029544; publication by Ivashchenko et al, 2020 [13]: Clinicaltrials.gov ID NCT04434248; preprint by Dabbous et al, 2020 [14]: clinicaltrials.gov ID NCT04349241. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [21], descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA), estimates on the outcome *Improvement in lung disease on CT up to 14 days* added by SNHTA.
Abbreviations: CI: Confidence interval; RR=relative risk.
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 the Ivashchenko study we considered the group Favipiravir 1600/600mg
b. Downgraded by two levels for high risk of performance bias and unclear risk of selection bias in all studies and reporting bias at high risk in one study and unclear in the other
c. Downgraded by one level for low number of events and small sample size
d. Downgraded by two levels for high risk of performance bias and unclear risk of selection bias and reporting bias
e. Downgraded by two levels for very small sample size and number of events
f. Downgraded of one level for small sample size
g. In the Ivashchenko study we considered the group Favipiravir 1600/600mg
h. Downgraded of two levels for high risk of performance and reporting bias and unclear risk of selection bias in all studies
i. Downgraded of two levels for very small sample size
j. In the Dabbous study, we used outcome data relating to a subgroup of patients: those with relevant CT chest findings at baseline. Improvement before day seven was extracted, outcome data on before day 15 was measured but not published.

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

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)	Number of participants (RCTs)	Certainty of evidence	Comments
	Risk with Umifenovir	Risk with favipiravir				
All cause mortality	-	-	Not estimable	236 (1)	low[a]	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)	236 (1)	very low[a,b]	

Source: publication by Chen et al, 2020 [22], related to Chinese Clinical Trial Registry ID ChiCTR200030254 / ChiCTR200030254. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [23], descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA).
Abbreviations: CI: Confidence interval; RR=relative risk.
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. Downgraded of two levels for high risk of performance bias and unclear risk of selection and reporting bias
b. Downgraded of one level for low number of events

Table 4-3 Summary of safety from observational studies (AE and SAE) of Favipiravir

Author, year	Cai 2020 [16]	Calik 2020 [11]
Country	China	Turkey
Sponsor	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
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

Author, year	Cai 2020 [16]	Calik 2020 [11]
RoB	High RoB Very low-quality evidence	High RoB Very low-quality evidence
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 (%)	-	-
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; ł** 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 4-4 Summary of safety from observational studies (AE and SAE) of Favipiravir

Author, year	Doi 2020 [19]
Country	Japan
Sponsor	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 cohort: 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
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	-#
Overall AEs, n (%)	Adverse events possibly or likely related to favipiravir use: 532/2158 (24.65%)
Serious AE (SAE), n (%)	-
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; # risk of bias not assessed, 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.
Abbreviations: FV = favipiravir; HQ = hydroxychloroquine AZ = azithromycin; L/R = Lopinavir/ritonavir; BID = twice daily

Table 4-5. Ongoing phase 3 trials of single agents: Favipiravir

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	Sponsor: Chelsea and Westminster Hospital NHS Foundation Trust, UK	Sponsor: ASST Fatebenefratelli Sacco	Sponsor: Zhejiang Hisun Pharmaceutical Co. Ltd.
Trial Identifier	EudraCT Number: 2020-001449-38 Clinicaltrials.gov: NCT04373733 Trial acronym: PIONEER	EUdraCT number: 2020-001115-25 ClinicalTrials.gov Identifier: NCT04336904 Other trial ID: HS216C17 Trial acronym: none	ClinicalTrials.gov Identifier: NCT04425460 EudraCT Number: 2020-001608-40 Other Study ID Numbers: HS216C17(MRCT) Trial acronym: none
Phase & Intention	Phase 3, early treatment Title*: A Randomised Controlled Trial of Early Intervention in Patients HospItalised With COVID-19: Favipiravir and StaNdard Care vErsEs Standard CaRe	Phase 3, treatment Title: A Multi-center, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of Patients With COVID-19-Moderate Type	Phase 3, treatment Title: A Multicenter, Randomized, Doubleblind, Placebo-controlled, Phase 3 Study Evaluating Favipiravir in Treatment of COVID19
Study design	Two-center two-arm randomised open label controlled trial with parallel group design*	Single center two-arm randomised double blind control trial with parallel group design	Multicenter two-arm randomised double blind trial with parallel group design
Status of trial	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)
Duration/End of Study	11 months* From May 1, 2020 to March 31, 2021*	4 months From 25 March 2020 to July 2020	4 months From June 2020 to September 2020
Study details			
Number of Patients	450	100	256
Disease severity	Not described, referred to hospital for period expected to last at least 1 day*	Moderate Covid-19	Moderate Covid-19
Setting	Hospitalized patients	Outpatient and hospitalised patients	Outpatient and hospitalised patients
Location/Centres	Two centers in London, United Kingdom	Single center in Milan, Italy	Multicenter with sites in China (n=2), Germany (n=2); Romania (n=4)
Intervention 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 (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
Duration of observation/ Follow-up	Up to day 28 post randomisation	Up to 90 days post randomisation	Up to day 28 post randomisation
Primary Outcomes	Primary efficacy endpoint: • Time to clinical improvement (post randomisation) by two points on a seven-	Primary efficacy endpoint: • Time from randomization to clinical recovery, up to 90 days	Primary efficacy endpoint: •Time from randomization to clinical recovery, up to 28 days

Active substance	Favipiravir	Favipiravir	Favipiravir
	category ordinal scale# or live discharge from the hospital, whichever comes first. Timepoint: until discharge from inpatient care, 28 day from enrolment or death		
Results/Publication	None, status 13 Nov. 20	None, status 14 Oct. 20	None, status 13 Nov. 20

For abbreviations see “List of abbreviations” at page 5.
*as described at clinicaltrials.gov; # = 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

Table 4-6 Ongoing phase 3 trials of single agents: Favipiravir, continued

Active substance	Favipiravir	Favipiravir Single & combination treatment	Favipiravir Single & combination treatment
Sponsor	Sponsor: Ain Shams University	Sponsor: Ministry of Health, Turkey	Beijing Chao Yang Hospital
Trial Identifier	ClinicalTrial.gov: NCT04349241 Trial acronym: FAV-001	ClinicalTrial.gov: NCT04411433 Trial acronym: none	ClinicalTrial.gov: NCT04319900 ChiCTR2000030987 Other trial ID: 2020-K-24-2 Trial acronym: none
Phase & Intention	Phase 3, treatment Title: Efficacy and Safety of Favipiravir in Management of COVID-19	Phase 3, treatment Title: Efficacy and Safety of Hydroxychloroquine and Favipiravir in the Treatment of Mild to Moderate COVID-	Phase 3, treatment Title: Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia
Study design	Single center, two-arm, randomised open label controlled trial with parallel group assignment	Multicenter, six-arm randomised open label controlled trial with parallel group assignment. Randomisation in 2:1:2:2:2:1 ratio	Multicenter three-arm randomised double blind controlled trial with parallel group assignment
Status of trial	Completed	Recruiting (last update posted 2 June 2020)	Recruiting (last update posted 24 March 2020)
Duration/End of Study	2 months From 18 April 2020 to 20 June 2020	2.5 months From 8 May 2020 to 30 July 2020 (planned)	3.5 months From 5 March 2020 to 25 June 2020
Study details			
Number of Patients	100	1000	150
Disease severity	Non-severe Covid-19 with mild to moderate symptoms according to the national egyptian protocol classification of patients	Mild to moderate Covid-19	Non-severe Covid-19
Setting	Not described	Not described	Not described
Location/Centres	Egypt, Cairo, 1 center	Turkey, Ankara, number of centers unclear	China, Beijing, centers not described

Active substance	Favipiravir	Favipiravir Single & combination treatment	Favipiravir Single & combination treatment
Intervention drug name and dosage	Favipiravir, 1600 mg bid on day 1, 600 mg bid on day 2 to day 10	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 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	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
Comparator (drug name and dosage)	Standard care: oseltamivir 75 mg bid for 5-10 days and hydroxychloroquine 400 mg bid on day 1 followed by 200mg bid on day 2 to day 5-10	Any of the active components above	Placebo, schedule not described
Duration of observation/ Follow-up	Up to 14 days	Up to 14 days	Up to 10 days post randomisation
Primary Outcomes	Primary efficacy outcome up to 14 days: •Viral clearance, defined as two successive negative COVID-19 PCR analysis tests 48-72 hours apart •Clinical improvement as defined by normal body temperature for 48 hours	Primary efficacy outcome up to 14 days • Time to recovery (discharge) • Decrease in viral load	Primary efficacy outcome up to 10 days: • Time of Improvement or recovery of respiratory symptoms • Number of days virus nucleic acid shedding • Frequency of Improvement or recovery of respiratory symptoms
Results/Publication	Published, status 14 Oct. 20 Outcome data will be considered in next update of this report.	None, status 13 Nov. 20	None, status 13 Nov. 20

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-7 Ongoing phase 3 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	Sponsor: R-Pharm	Shahid Beheshti University of Medical Sciences	FUJIFILM Toyama Chemical Co., Ltd.
Trial Identifier	ClinicalTrials.gov Identifier: NCT04501783	Iranean registry of Randomised Trials (IRCT) registration number: IRCT20151227025726N14	JPRN-JapicCTI-205238
Phase & Intention	Phase 3, treatment Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients With Mild to Moderate COVID-19	Treatment Phase 3 Title: Evaluation the efficacy and safety of Favipiravir made by Shahid Beheshti University of Medical Sciences in comparison with Lopinavir-ritonavir in COVID-19 patients	Treatment Phase 3 Title: Multicenter, Adaptive, Randomized, Placebo-Controlled, Comparative Study to Evaluate the Efficacy and Safety of Favipiravir in Patients with COVID-19 Non-Severe Pneumonia
Study design	Multicenter, 2-arm randomised open label controlled trial with parallel group assignment. •Allocation: Randomized 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)	Single center, 2-arm randomised open label controlled trial with parallel group assignment. Block randomization, with block size of four.	Multicenter, Adaptive, Randomized, Placebo-Controlled, Comparative Study
Status of trial	Active, not recruiting (last update at registry on 6 of Aug. 2020)	Unknown (last update at registry on 4th of July 2020)	Ongoing, recruitment completed (last update at registry 1 Sept. 2020)
Duration/End of Study	August 2020	End of recruitment planned at 7 July 2020	30 June 2020 (planned)
Study details			
Number of Patients	168	84	96
Disease severity	Mild to moderate COVID-19	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	Patients with COVID-19 non-severe pneumonia
Setting	In and outpatients	Hospitalised	Hospitalised
Location/Centres	Russia, 10 centers in Moscow, Saint Petersburg, Korolev, Voronezh and Zhukovskiy	Iran, Tehran	Japan

Active substance	Favipiravir	Favipiravir	Favipiravir
Intervention drug name and dosage	Favipiravir Day 1: favipiravir 1800 mg BID plus Standard of Care (SOC); Days 2-10: 800 mg BID plus SOC	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.	Favipiravir (T-705), Oral Multiple Dose, not further defined & standard care
Comparator (drug name and dosage)	Standard of Care	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.	Standard care, not further defined
Duration of observation/ Follow-up	Up to day 28	Up to day 14	Not described
Primary Outcomes	• Time to clinical improvement [Time Frame: through Day 28] • Time to viral clearance [Time Frame: through Day 28]	• Fever through Day 14 • Cough through Day 14 • Dyspnea through Day 14	• 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
Results/Publication	None, status 13 Nov. 20	None, status 14 Oct. 2020	None, status 14 Oct. 2020

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-8 Ongoing phase 3 trials of single agents: Favipiravir, continued

Active substance	Favipiravir	Favipiravir	Favipiravir
Sponsor	Istituto Nazionale Per Le Malattie Infettive (INMI) "Lazzaro Spallanzani" – Rom, Italy	Dr. Reddy's Laboratories Limited	Promomed, LLC
Trial Identifier	EudraCT number: 2020-001528-32 Other identifier: ARCO-Homestudy	ClinicalTrials.gov Identifier: NCT04529499	ClinicalTrials.gov Identifier: NCT04542694 Other Study ID Numbers: FAV052020
Phase & Intention	Treatment Phase 3 Title: Adaptive Randomized trial for therapy of COrona virus disease 2019 at home with oral antivirals (ARCO-Home study)	Treatment Phase 3 Title: A Multi-center, Randomized, Double Blind, Placebo Controlled Clinical Trial Evaluating the Efficacy and Safety of Favipiravir in Moderate to Severe COVID-19 Patients	Treatment Phase 3 Title: Open-label Randomized Multicenter Comparative Study on the Efficacy and Safety of Areplivir Film-coated Tablets (PROMOMED RUS LLC, Russia) in Patients Hospitalized With COVID-19
Study design	Multicenter, 5-arm randomized open label controlled trial with adaptive design	Multicenter, 2-arm randomized double blind placebo controlled trial with parallel group assignment. Blinding of participants, care providers, investigators and outcomes Assessors.	Multicenter, 2-arm randomized open label controlled trial with parallel group assignment.

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Status of trial	Ongoing (last update at registry on 24 June 2020)	Recruiting (last update at registry on 18 Sept. 2020)	Completed (last update at registry on 5 Nov. 2020)
Duration/End of Study	3 month duration	31 January 2021 (planned end of study)	20 August 2020 (actual end of trial)
Study details			
Number of Patients	Minimal 175 to maximal 435 (adaptive design)	780	200
Disease severity	Symptomatic, not meeting criteria for immediate hospitalization (national early warning score-NEWS = 2 criteria)	Moderate to severe	Mild to moderate
Setting	outpatients	quarantined in an institutional quarantine facility or hospitalised	hospitalised
Location/Centres	Italy, 5 sites	Kuwait, Kuwait city, 2 centers	Russia, 5 centers
Intervention 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 (Areplivir): 1600 mg (8 tablets) on day 1, BID; 600 mg (3 tablets) BID on day 2-14.
Comparator (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 of 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. Might include hydroxychloroquine (with or without azithromycin), chloroquine, lopinavir/ritonavir or other recommended schemes.
Duration of observation/ Follow-up	Up to day 14	Main phase of trial: up to 28 (+2) days or until discharge from the hospital/institutional quarantine facility, whichever is earlier. Extended phase of trial: up to day 60	Up to 28 days

Active substance	Favipiravir	Favipiravir	Favipiravir
Primary Outcomes	• 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 clinical improvement [Time Frame: 10 days]: time (in days) to improvement in clinical status by WHO categorical ordinal scale of clinical status improvement. • Rate of clinical status improvement [Time Frame: 10 days]: rate of clinical status improvement by categorical ordinal scale of clinical status improvement by 2 or more categories by Day 10
Results/Publication	None, status 14 Oct. 2020	None, status 13 Nov. 2020	Study results posted at clinicaltrials.gov/ct2/show/results/NCT04542694, status 13 Nov. 2020

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-9 Ongoing phase 3 trials of single agents: Favipiravir, continued

Active substance	Favipiravir	Favipiravir	Favipiravir
Sponsor	Indonesia University	Hungarian Ministry of Innovation and Technology - Representative: Hecrin Consortium	Glenmark Pharmaceuticals Ltd, India
Trial Identifier	ClinicalTrials.gov Identifier: NCT04558463	EudraCT Identifier: 2020-002728-35 Sponsor Protocol Number: HUN-AVI-01	Clinical Trials Registry-India Identifier: CTRI/2020/05/025114 Sponsor Protocol Number: GPL/CT/2020/002/III, Version: 3.0, dated: 26 Apr 2020
Phase & Intention	Phase 3, Treatment Title: The Effectivity and Safety of Favipiravir Compared to Oseltamivir as Adjuvant Therapy for COVID-19: An Open Label Trial	Phase 3, Treatment Title: An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients with Mild Pneumonia − An open-label randomized controlled study	Phase 3, Treatment Title: A Randomized, Open-label, multicenter study to evaluate the efficacy and safety of Favipiravir combined with STANDARD supportive care in adult Indian patients with mild to moderate COVID-19
Study design	Two arm open label randomized controlled trial with parallel group assignment	Two arm open label multicenter randomized controlled trial with parallel group assignment	Two arm open label randomized controlled trial with parallel group assignment. Use of centralized randomization, randomization stratified by baseline disease severity.

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Status of trial	Recruiting (last update at registry on 22 Sept. 2020)	Ongoing (last update at registry on 13 Aug. 2020)	(last update at registry on 27 July 2020)
Duration/End of Study	30 October 2020	10 months	1 year, first patient enrolled at 20 May 2020
Study details			
Number of Patients	100 (planned)	150	150
Disease severity	Covid-19 patients with mild, moderate and severe symptoms	Patients with new type of coronavirus (SARS-CoV-2) infection proven by RT-PCR test with mild pneumonia.	Mild to moderate COVID-19
Setting	Hospital	Not described	Hospital
Location/Centres	Cipto Mangunkusumo National Referral Hospital, Jakarta, DKI Jakarta, Indonesia	Hungary, six sites	India, 12 sites
Intervention 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 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	Favipiravir (avigan): use of 200 mg tablets for oral use, dosage and duration not described	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).
Comparator (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	Standard supportive care, not further described.
Duration of observation/ Follow-up	21 days of follow-up	Up to 28 days of follow-up	Up to 28 days of follow-up
Primary Outcomes	• 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.	• Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days]. Details: time in days from randomization to a negative SARS-CoV2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab
Results/Publication	None, status 13 Nov. 2020	None, status 14 October 2020	None, status 14 October 2020

For abbreviations see “List of abbreviations” at page 5.

Table 4-10 Ongoing phase 3 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**
Sponsor	Appili Therapeutics Inc.	University of Pecs, Hungary
Trial Identifier	ClinicalTrials.gov Identifier: NCT04600895 Other Study ID Numbers: PRESECO	ClinicalTrials.gov Identifier: NCT04600999 Other Study ID Numbers: HUN-AVI-01
Phase & Intention	Phase 3, treatment Title: Favipiravir for Patients With Mild to Moderate Disease From Novel Coronavirus (COVID-19)	Phase 3, treatment Title: An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients With Mild Pneumonia - An Open-label Randomized Controlled Study
Study design	Triple blinded two-arm open label randomized controlled trial with parallel group assignment. Masking of participant, care provider and investigator.	Multicenter two-arm open label randomized controlled trial with parallel group assignment.
Status of trial	Not yet recruiting (last update at registry on 23 Oct. 2020)	Recruiting (last update at registry on 23 Oct. 2020)
Duration/End of Study	October 2021 (planned)	June 2021 (planned)
Study details		
Number of Patients	826	150
Disease severity	mild-moderate COVID-19 patients	Moderate COVID-19 patients with mild pneumonia
Setting	outpatients	Hospital
Location/Centres	No contacts or locations provided	5 centers in Hungary
Intervention 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.
Comparator (drug name and dosage)	Placebo	Supportive care, defined as symptomatic therapy.
Duration of observation/ Follow-up	Up to 21 days of follow-up	Up to 9 months of follow-up
Primary Outcomes	• 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
Results/Publication	None, status 13 Nov. 2020	None, status 13 Nov. 2020

For abbreviations see “List of abbreviations” at page 5.

Table 4-11. Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	King Abdullah International Medical Research Center	Ministry of Health, Turkey	Appili Therapeutics Inc.
Trial Identifier	ClinicalTrials.gov Identifier: NCT04464408 Acronym: Avi-Mild	ClinicalTrials.gov Identifier: NCT04474457 Other Ids: COVID-19-PMSFAV Title: Efficacy and Safety of Favipiravir in the Treatment of COVID-19 Patients Over 15 Years of Age	ClinicalTrials.gov Identifier: NCT04448119 Other Ids: CONTROL-COVID-Favipiravir-1 Title: Control of COVID-19 Outbreaks in Long Term Care
Phase & Intention	Phase 2, Phase 3, treatment Title: Favipiravir Therapy in Adults With Mild COVID-1	Phase not specified, observational	Phase 2, early treatment/prophylaxis
Study design	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Study Design: •Observational Model: Cohort •Time Perspective: Prospective	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Prevention
Status of trial	Recruiting (last update at trial registry 9 Sept. 2020)	Recruiting (last update at trial registry 20 July 2020)	Recruiting (last update at trial registry 23 Oct. 2020)
Duration/End of Study	From July 2020 to June 2021	From June 11, 2020 to September 30, 2020	From June 2020 to March 2021
Study details			
Number of Patients	578	1000	760
Disease severity	Mild COVID-19	Not described	Not described, likely from no disease to severe disease
Setting	Not described	Not described	Long-term care homes
Location/Centres	Not described/ Saudi Arabia	Turkey, Ankara, 14 centers	Not described
Intervention 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	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 (drug name and dosage)	Placebo	None	Placebo: 8 tablets orally twice daily on day 1, followed by 4 tablets twice daily from days 2-25.

	9 tablets by mouth twice daily for one day, followed by 4 tablets twice daily (Maximum days of therapy is 7 days)		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
Duration of observation/ Follow-up	Up to 28 days after randomization	Up to 7 days	Up to 60 days
Primary Outcomes	Primary efficacy outcome: • PCR negative [Time Frame: 15 days]	Primary efficacy outcome: • Time to recovery (discharge) [Time Frame: 7 days] • Decrease in viral load [Time Frame: 7 days]	Primary efficacy outcome: • Control of Outbreak [Time Frame: Day 40]
Results/Publication	None, status 13 Nov. 20	None, status 13 Nov. 20	None, status 13 Nov. 20

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-12 Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	Fujifilm Pharmaceuticals U.S.A., Inc.	Royal College of Surgeons in Ireland - Medical University of Bahrain	Chromis LLC
Trial Identifier	ClinicalTrials.gov Identifier: NCT04358549 Other Ids: FAVI-COV-US201	ClinicalTrials.gov Identifier: NCT04387760 Other Ids: 40 / 07-May-2020	ClinicalTrials.gov Identifier: NCT04434248 Other Ids: COVID-FPR-01
Phase & Intention	Phase 2, treatment Title: Study of the Use of Favipiravir in Hospitalized Subjects With COVID-19	Phase 2, treatment Title: Favipiravir vs Hydroxychloroquine in COVID-19	Phase 2/3, treatment Title: An Adaptive Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19
Study design	Open label, randomized (1:1 ratio), controlled, multicenter Phase 2 proof-of-concept study, with parallel group assignment	Randomized open label randomized controlled trial with parallel group assignment	Adaptive, multicenter, open-label, randomized clinical study (Sequential Assignment)
Status of trial	Active, not recruiting (last update at trial registry 6 Nov. 2020)	Recruiting (last update at trial registry 18 Aug. 2020)	Active, not recruiting (last update at trial registry 16 June 2020)
Duration/End of Study	1 November 2020 (planned end of study)	From August 14, 2020 to May 14, 2021	July 2020
Study details			
Number of Patients	50 (actual)	150	330

Disease severity	Not described	Mild to moderate COVID-19	Moderate to severe COVID-19
Setting	Inpatients	Inpatients	Inpatients
Location/Centres	United States, 8 centers in Arizona, Florida, Massachusetts, New Jersey and Texas	Ireland, Bahrain, Manama	Russian Federation, mutiple centres in Makhachkala, Moscow, Nizhny Novgorod, Ryazan, Saint Petersburg, Saratov, Smolensk, Tver, Ufa, Yakutsk, Yaroslavl
Intervention 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 (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.
Duration of observation/ Follow-up	Up to 29 days	Up to 30 days	Up to 28 days
Primary Outcomes	• 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]

Results/Publication	None, status 9 Nov. 20	None, status 13 Nov. 20	Interim report published [13], status 14 Oct. 20. Outcome data from the interim report are included in the Summary of Findings Table 4-1

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-13 Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor/Collaborator	Stanford University	Bangladesh Medical Research Council (BMRC)	Bayside Health
Trial Identifier	ClinicalTrials.gov Identifier: NCT04346628 Other Study ID Numbers: 56032	ClinicalTrials.gov Identifier: NCT04402203 Other Study ID Numbers: 29318042020	ClinicalTrials.gov Identifier: NCT04445467 Acronym: VIRCO
Phase & Intention	Phase 2, early treatment Title: A Phase 2 Randomized, Double Blinded, Placebo Controlled Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild or Asymptomatic COVID-19	Phase 2, treatment Title: Study on Safety and Efficacy of Favipiravir (Favipira) for COVID-19 Patient in Selected Hospitals of Bangladesh	Phase 2, treatment Title: An Adaptive Randomised Placebo Controlled Phase II Trial of Antivirals for COVID-19 Infection
Study design	Randomized double blinded placebo controlled trial with parallel group assignment	Multicenter double-blind, placebo-controlled randomized control study with parallel group assignment	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment
Status of trial	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)
Duration/End of Study	July 2021 (planned end of study)	July 2020 (planned end of study)	November 2020
Study details			
Number of Patients	120	50	190
Disease severity	Mild or asymptomatic COVID-19	Mild to moderate COVID-19	Not described
Setting	Not described	Inpatients	In and outpatients

Location/Centres	United States, California, 1 center	Bangladesh, Dhaka, 4 centers	Not described
Intervention 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 (drug name and dosage)	In addition to SOC, placebo to match favipiravir for 10 days	Standard Treatment	Placebo
Duration of observation/ Follow-up	Up to 28 days	Up to 10 days	Up to 28 days
Primary Outcomes	• 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 Frame: at Day-4, Day-7 and Day-10 of therapy]	• Time to virological cure [Time Frame: 14 days]
Results/Publication	None, status 13 Nov. 20	None, status 13 Nov. 20	None, status 13 Nov. 20

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-14 Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	Peking University First Hospital	NHS Greater Glasgow and Clyde / The University of Glasgow, UK	University College London Comprehensive Clinical Trial Unit, UK
Trial Identifier	ClinicalTrials.gov Identifier: NCT04310228 Chinese Clinical Trial Registry ID: ChiCTR2000030894	EudraCT Number: 2020-001904-41 ISRCTN identifier: ISRCTN31062548 Trial acronym: GETAFIX	EudraCT number: 2020-002106-68 ClinicalTrials.gov Identifier: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals
Phase & Intention	Phase not described, treatment Title: Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	Phase 2, early treatment Title: Glasgow Early Treatment Arm FavIpiravir: A randomized controlled study of favipiravir as an early treatment arm in COVID-19 patients	Phase 2, early treatment Title: Favipiravir, lopinavir/ritonavir or combination therapy: a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Study design	Multicenter three-arm open label randomized controlled trial with parallel group assignment	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.	Multicenter, randomised, double-blind, 2x2 factorial placebo-controlled trial Masking: triple (participant, care provider, investigator)
Status of trial	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)
Duration/End of Study	May 2020 (planned end of study)	May 2021	From 24 September 2020 to 1 March 2021
Study details			
Number of Patients	150	302	240
Disease severity	Not described, cases of respiratory failure and requiring mechanical ventilation were excluded	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	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
Setting	Not described	In and outpatients	Not described, likely outpatients
Location/Centres	China, 6 centers in Beijing and Hubei	Single center in Glasgow, United Kingdom	UK, 4 sites
Intervention 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	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

Active substance	Favipiravir	Favipiravir	Favipiravir
	maximum single dose does not exceed 800mg		
Comparator (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.*
Duration of observation/ Follow-up	Up to 3 months	Up to 60 days of follow-up	Up to 28 days of follow-up
Primary Outcomes	• Clinical cure rate [Time Frame: 3 months]	• 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
Results/Publication	None, status 13 Nov. 20	None, status 13 Nov. 20	None, status 13 Nov. 20

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-15 Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	Favipiravir	Favipiravir	
Sponsor	Peking University First Hospital	Tanta University	
Trial Identifier	ClinicalTrials.gov Identifier: NCT04333589 Other Study ID Numbers: 2020 research 112	ClinicalTrials.gov Identifier: NCT04351295 Other Study ID Numbers: faviprevir covid	
Phase & Intention	Not described, treatment Title: Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive	Phase 2/3, treatment Title: Clinical Study Evaluating the Efficacy of Faviprevir in COVID-19 Treatment	
Study design	Multicenter randomized open label controlled trial with parallel group assignment	Multicenter randomized open label controlled trial with parallel group assignment	

Status of trial	Recruiting (last update at trial registry: 24 April 2020)	Recruiting (last update at trial registry: 29 Sept. 2020)	
Duration/End of Study	15 September 2020 (planned end of study)	December 1, 2020	
Study details			
Number of Patients	210	90	
Disease severity	Not described	Not described	
Setting	Not described	Not described	
Location/Centres	China, 8 centers in Anhui, Hubei and Zhejiang	Egypt, Tanta, 1 center listed	
Intervention 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	
Comparator (drug name and dosage)	Regular treatment group	Placebo	•
Duration of observation/ Follow-up	Up to 5 months	Up to 6 months	
Primary Outcomes	Primary efficacy outcome: • Viral nucleic acid test negative conversion rate [Time Frame: 5 months]	Primary efficacy outcome: • Number of patients with mortality or need for mechanical ventilation	•
Results/Publication	None, status 13 Nov. 20	None, status 13 Nov. 20	

For abbreviations see “List of abbreviations” at page 5. *as described at clinicaltrials.gov

Table 4-16 Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	The First Affiliated Hospital, Zhejiang University School of Medicine	The Third People's Hospital of Shenzhen	Beijing Chaoyang Hospital, Capital Medical University
Trial Identifier	Chinese Clinical Trial Registry ID: ChiCTR2000029548	Chinese Clinical Trial Registry ID: ChiCTR2000030113	Chinese Clinical Trial Registry ID: ChiCTR2000029996
Phase & Intention	Treatment Title: Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	Treatment Title: Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir	Treatment Phase 2 Title: A randomized, open-label, controlled trial for the efficacy and safety of Farpiravir Tablets in the treatment of patients with novel coronavirus pneumonia (COVID-19)

Study design	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.	Three arm randomized open label controlled trial with parallel group assignment
Status of trial	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)
Duration/End of Study	end 3 June 2020 (planned)	end 31 May 2020 (planned)	20 April 2020 (planned end of study)
Study details			
Number of Patients	30	30	60
Disease severity	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	Any, corona pneumonia with poorly responsive ritonavir Randomised to ritonavir or favipiravir	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	Not described	Not described, likely hospitalised	Hospitalised
Location/Centres	China, province Zhejiang, city Hangzhou	China, Shenzhen, Guangdong	China, Beijing
Intervention 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 2400 mg per time on first day; the duration of treatment will be 10 d.
Comparator (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
Duration of observation/ Follow-up	Up to 28 days of follow-up	Not reported	Up to 10 days of follow-up

Primary Outcomes	• 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"
Results/Publication	None, status 14 Oct. 20	None, status 10 Sept. 2020	None, status 10 Sept. 20

For abbreviations see "List of abbreviations" at page 5. *as described at clinicaltrials.gov

Table 4-17 Ongoing phase 2 trials of single agents: Favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor	Fujita Medical University Hospital	Zhongnan Hospital of Wuhan University	Faculty of Medicine, Siriraj Hospital
Trial Identifier	Japan Register of Clinical Trials: JPRN-jRCTs041190120	Chinese Clinical Trial Registry ID: ChiCTR2000030254	Thai Clinical Trial Registry: TCTR20200514001
Phase & Intention	Treatment Phase 2 Title: A multicenter, open-label, randomized clinical trial of favipiravir aimed at examining the viral load reduction effect in asymptomatic and mildly ill patients with SARS-CoV2 infection	Treatment Phase not specified Title: The Efficacy and Safety of Favipiravir for novel coronavirus–infected pneumonia: A multicenter, randomized, open, positive, parallel-controlled clinical study	Treatment Phase 2 / 3 Title: An Investigation of the Efficacy and Safety of Favipiravir in COVID-19 Patients without Pneumonia − An open-label randomized controlled study
Study design	Two-arm randomized open label controlled trial with parallel group assignment.	Randomised, open label, controlled trial with parallel group assignment.	Two-arm open-label randomized placebo controlled trial with parallel group assignment
Status of trial	completed	Recruitment completed	Pending, not yet recruiting (last updated at trial registration: 13 May 2020)
Duration/End of Study	31 August 2020 (planned end of study)	20 March 2020 (planned end of study)	March 31, 2021 (planned end of study)
Study details			
Number of Patients	89	240	96
Disease severity	Asymptomatic and mild	Not reported. Severe patients with expected survival time < 48 hours are excluded	Mild or moderate COVID-19
Setting	Not described	Hospitalised	Not described
Location/Centres	Japan Lead center Fujita Health University Hospital	China, Hubei	Thailand

Intervention drug name and dosage	• Immediate favipiravir arm: 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	Favipiravir ("Farpiravir tablets"), 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 (drug name and dosage)	• Delayed favipiravir arm: 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	Arbidol ("abidole tablets"), not further descibed	Supportive care: symptomatic therapy not further defined for 4 days (maximum)
Duration of observation/ Follow-up	Up to 10 days of follow-up	Unclear, at least up to 7 days	Up to day 28
Primary Outcomes	• 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	• Clinical recovery rate of day 7	• Time to improvement in body temperature and SpO2 without chest imaging findings, and negative SARS-Cov2 through day 28
Results/Publication	Summary outcome data posted on Registry Site. Peer reviewed or pre-print version not yet identified (status 10 Sept. 2020)	Published at preprint server, status 13 November 2020 [11]	None, status 13 Nov. 2020

For abbreviations see "List of abbreviations" at page 5. *as described at clinicaltrials.gov

Table 4-18 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir

Active substance	**Favipiravir and Hydroxychloroquine**	**Favipiravir and Hydroxychloroquine**	**Favipiravir/Hydroxychloroquine**
Sponsor	Shahid Beheshti University of Medical Sciences	King Abdullah International Medical Research Center	Baqiyatallah Medical Sciences University
Trial Identifier	NCT04359615 Trial acronym: FIC	ClinicalTrial.gov: NCT04392973 Trial acronym: FACCT - FAvipiravir and HydroxyChloroquine Combination Therapy Other Study ID Numbers: RC20/174	ClinicalTrials.gov Identifier: NCT04376814
Phase & Intention	Phase 3 (described by trial authors as phase 4)	Phase not described, Treatment Title: A Trial of Favipiravir and Hydroxychloroquine Combination in	Phase not described, treatment Short title: Favipiravir Plus Hydroxychloroquine and

Active substance	Favipiravir and Hydroxychloroquine	Favipiravir and Hydroxychloroquine	Favipiravir/Hydroxychloroquine
	Title: Favipiravir in Hospitalized COVID-19 Patients	Adults Hospitalized With Moderate and Severe Covid-19	Lopinavir/Ritonavir Plus Hydroxychloroquine in COVID-19
Study design	Single center 2-arm randomised triple blinded controlled trial with parallel group design	Multicenter, open label, randomised controlled trial in parallel design	Non-randomized open label controlled trial with parallel group assignment
Status of trial	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)
Duration/End of Study	From 20 April 2020 to 5 May 2020 (planned)	From 21 may 2020 to November 2021	May 25, 2020 (actual)
Study details			
Number of Patients	40	520	40
Disease severity	Not described	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 Chest X ray changes that require hospital admission	Not described, requiring hospitalization
Setting	Hospitalized	Hospitalised	Inpatients
Location/Centres	Iran, Tehran 1 center	Saudi Arabia, 8 sites	Iran, Tehran
Intervention 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 (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
Duration of observation/ Follow-up	Up to 14 days of follow-up	Up to 28 days of follow-up	Up to 28 days
Primary Outcomes	• •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	• Mortality [Time Frame: Up to 28 days] • long of hospitalization [Time Frame: Up to 28 days] • Laboratory Treatment Response (Blood cell count) [Time Frame: Up to 28 days]

Active substance	Favipiravir and Hydroxychloroquine	Favipiravir and Hydroxychloroquine	Favipiravir/Hydroxychloroquine
		discharge from the hospital, whichever came first.	• Laboratory Treatment Response (CRP) [Time Frame: Up to 28 days] • Dyspnea [Time Frame: Up to 28 days] • Oxygen saturation without supplemental oxygen. [Time Frame: Up to 28 days] • Oxygen therapy [Time Frame: Up to 28 days]
Results/Publication	None, status 13 Nov. 20	None, status 13 Nov. 20	None, status 13 Nov. 20

Table 4-19 Ongoing trials of combination therapies including Favipiravir & Hydroxychloroquine ± Lopinavir /Ritonavir, continued

Active substance	Favipiravir/Hydroxychloroquine	favipiravir + hydroxychloroquine	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine
Sponsor	Iran university of medical sciences Second sponsor: Bagheiat-allah University of Medical Sciences	Quality Improvement of Intensive Care Research Center- Shahid Beheshti University	Rajavithi Hospital
Trial Identifier	Iranean registry of Randomised Trials (IRCT) registration number: IRCT20200318046812N1	Iranean Registry of Randomised Trials (IRCT) registration number: IRCT20200428047228N1	ClinicalTrials.gov Identifier: NCT04303299 Acronym: previously THDMS-COVID-19; currently fight COVID-19
Phase & Intention	Treatment Phase 3 Title: Evaluation of safety and efficacy of hydroxychloroquine plus favipiravir drug regimen in comparison with hydroxychloroquine plus kaletra on the need for intensive care unit treatment in patients with COVID-19; a randomized, multicenter, parallel groups, open label study	Treatment Phase 3 Title: Evaluation of the efficiency and safety of favipiravir + hydroxychloroquine drug regimen in comparison with hydroxychloroquine in hospitalized patients with covid-19	Phase 3, treatment Title (new title): Favipiravir, Protease Inhibitors, Oseltamivir -Gpo, Hydroxychloroquine for Treatment of COVID-19 (FIGHT-COVID-19)
Study design	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.	Double blinded randomized controlled trial with parallel group assignment. Masking of participants, care providers & outcome assessors. Simple randomization using a Random Number Table	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.

Active substance	**Favipiravir/Hydroxychloroquine**	**favipiravir + hydroxychloroquine**	**Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine**
Status of trial	Recruitment completed (last update at registry: 26 August 2020)	Recruitment complete (last update at registry: 16 May 2020)	Recruiting (last update at trial registry 1 Sept. 2020)
Duration/End of Study	Not reported	Not reported	31 December 2021
Study details			
Number of Patients	324	50	320
Disease severity	Diagnosis of COVID-19 based on either ground glass appearance in chest CT scan or positive RT-PCR test for COVID-19; Requiring hospitalization	Not reported	Mild to critical COVID-19
Setting	Hospitalised	Hospitalised	In- and outpatients
Location/Centres	Iran, 20 centers all over the country	Iran	Thailand, Bangkok
Intervention 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
Comparator (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

Active substance	Favipiravir/Hydroxychloroquine	favipiravir + hydroxychloroquine	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine
			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”
Duration of observation/ Follow-up	Not described	Not described	Up to 24 weeks
Primary Outcomes	• Admission to intensive care unit	• No fever for 3 days • SpO2>93% • CXR observation	• SARS-CoV-2 eradication time [Time Frame: Up to 24 weeks]
Results/Publication	None, status 14 Oct. 2020	None, status 14 Oct. 2020	None, status 13 Nov. 20

Table 4-20 Ongoing trials of combination therapies including Favipiravir and Lopinavir/ritonavir

Active substance	**Favipiravir (Avigan) and + Kaletra (Lopinavir/ritonavir)**
Sponsor	University College London Comprehensive Clinical Trial Unit, UK
Trial Identifier	EudraCT number: 2020-002106-68 ClinicalTrials.gov Identifier: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals
Phase & Intention	Phase 2 Early treatment Title: Favipiravir, lopinavir/ritonavir or combination therapy: a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19
Study design	Multicenter, randomised, double-blind, 2x2 factorial placebo-controlled trial Masking: triple (participant, care provider, investigator)
Status of trial	Not yet recruiting (last update at trial registry 5 Aug. 2020*)
Duration/End of Study	From 17 August 2020 to 1 March 2021
Study details	
Number of Patients	240
Disease severity	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	Not described, likely outpatients
Location/Centres	UK, 4 sites
Intervention 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 (drug name and dosage)	Matched Placebo, oral intake, dosing scheme and mg identical to Avigan and Kaletra schemes.*
Duration of observation/ Follow-up	Up to 28 days of follow-up
Primary Outcomes	• upper respiratory tract viral load at Day 5 as measured with quantitative polymerase chain reaction (PCR) performed on saliva samples
Results/Publication	None, status 13 Nov. 20

Table 4-21 Ongoing trials of combination therapies including Favipiravir and Tocilizumab

Active substance	**Favipiravir Combined With Tocilizumab**
Sponsor	Peking University First Hospital
Trial Identifier	ClinicalTrials.gov Identifier: NCT04310228 Chinese Clinical Trial Registry ID: ChiCTR2000030894 Other study ID: 2020YFC0844100
Phase & Intention	Phase not described, treatment Title: Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019
Study design	Multicenter 3-arm randomized open label controlled trial with parallel group assignment
Status of trial	Recruiting (last update at trial registry 10 April 2020)
Duration/End of Study	May 2020 (planned end of study)
Study details	
Number of Patients	150
Disease severity	Likely mild to moderate, excluded who required hospitalization
Setting	outpatients
Location/Centres	China, 6 centers in Beijing and Hubei
Intervention drug name and dosage	• Favipiravir group: 1600mg BID on day 1, 600mg BID on day 2-7 (maximum). Oral administration. • Favipiravir Combined With Tocilizumab group: Favipiravir: 1600mg BID on day 1, 600mg BID on day 2-7 (maximum). Oral administration. Tocilizumab: The first dose is 4 ~ 8 mg/kg and the recommended dose is 400mg. 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 800 mg
Comparator (drug name and dosage)	• Tocilizumab group: the first dose is 4 ~ 8 mg/kg and the recommended dose is 400mg. 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.
Duration of observation/ Follow-up	Up to 3 months
Primary Outcomes	• Clinical cure rate [Time Frame: 3 months]
Results/Publication	None, status 13 Nov. 20

Table 4-22 Ongoing trials of combination therapies including Favipiravir and other antiviral substances: Umifenovir or Maraviroc

Active substance	**Favipiravir & Umifenovir**	**Maraviroc & Favipiravir**
Sponsor	Glenmark Pharmaceuticals Ltd, India	Hospital General de México Dr. Eduardo Liceaga
Trial Identifier	Clinical Trials Registry-India Identifier: CTRI/2020/06/025957 Sponsor Protocol Number: GPL/CT/2020/004/III, Version:4.0, Dated:03-Jun-2020	ClinicalTrials.gov Identifier: NCT04475991 Acronym: COMVIVIR
Phase & Intention	Phase 3, Treatment Title: A Randomized Open-Label Study To Evaluate The Efficacy And Safety Of Favipiravir And Umifenovir As Compared To Favipiravir Alone In Moderate Hospitalized Adult Indian COVID-19 Patients.	Phase 2, treatment Title: Safety and Efficacy of Maraviroc and/or Favipiravir vs Currently Used Therapy in Severe COVID-19 Adults
Study design	Two arm open label randomized controlled trial with parallel group assignment. Use of centralized computer based randomization	Randomized open label controlled trial with parallel group assignment
Status of trial	Open to recruitment (last update at registry on 14 Sept. 2020)	Not yet recruiting (last update at trial registry 4 Nov. 2020)
Duration/End of Study	6 months, first patient enrolled at 29 June 2020	January 2021
Study details		
Number of Patients	158	100
Disease severity	moderate COVID-19, hospitalised	Severe COVID-19
Setting	Hospital	Inpatients
Location/Centres	India, 20 sites	Mexico, Mexico City
Intervention drug name and dosage	Arm 1: favipiravir, umifenovir 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) combined with • Umifenovir: use of oral capsules of 800 mg, BID (1,600 mg) Standard supportive care, not further described	• 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). 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).
Comparator (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	• Maraviroc + Currently used therapy: Maraviroc tablets. 300 mg bid, given orally for a 10 day period AND Currently used therapy Currently used therapy for COVID-19 non-critical patients: Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga"
Duration of observation/ Follow-up	Up to 28 days of follow-up	Up to 28 days

Active substance	Favipiravir & Umifenovir	Maraviroc & Favipiravir
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]
Results/Publication	None, status 13 Nov. 2020	None, status 9 Nov. 20

Table 4-23 Ongoing trials of combination therapies including Favipiravir and other substances: Nafamostat Mesilate or Nitazoxanide

Active substance	Favipiravir + Nafamostat Mesilate	Favipiravir + Nitazoxanide
Sponsor	Not reported, likely the University of Tokyo	Shin Poong Pharmaceutical Co. Ltd.
Trial Identifier	Japan Registry of Clinical Trials ID: jRCTs031200026	ClinicalTrials.gov Identifier: NCT04532931 Other Study ID Numbers: SP-PA-COV-202
Phase & Intention	Treatment Phase not described Title: Multicenter, Single blinded Randomized Controlled, Comparative Study to Evaluate the Efficacy and Safety of Favipiravir and Nafamostat Mesilate in Patients with COVID-19 Pneumonia	Treatment Phase 2 Title: Phase 2, Exploratory, Single Center, Randomized, Open Label, Adaptive Clinical Trial to Compare Safety and Efficacy of Four Different Experimental Drug Regimens to Standard of Care for the Treatment of Symptomatic Outpatients With COVID-19
Study design	Multicenter, Single blinded Randomized Controlled, Comparative Study with parallel group assignment	Randomized, adaptive, single center open label controlled trial with parallel group design.
Status of trial	Recruiting (last update at registry: 28 August 2020)	Recruiting (last update at registry: 8 Oct. 2020)
Duration/End of Study	Not reported	January 21 (planned end of study)
Study details		
Number of Patients	160	250
Disease severity	COVID-19 with pneumonia. Excluded are patients “having less than 93% of oxygen saturation (SpO2) in without the oxygen administration”	Mild
Setting	Likely hospitalised	Outpatients
Location/Centres	Japan, Tokyo	South Africa, Johannesburg: single center
Intervention drug name and dosage	• Favipiravir and Nafamostat Mesilate & standard treatment not further specified	All experimental arms also receive standard of care (SOC) as described in the comparator. • Artesunate + Amodiaquine arm: SOC plus artesunate-amodiaquine (ASAQ) - 2 tablets (200/540 mg artesunate/amodiaquine) daily for 3 days • Pyronaridine + Artesunate arm: SOC plus pyronaridine-artesunate (PA) Weight 45 to <65 kg: 3 tablets (540/180 mg

Active substance	Favipiravir + Nafamostat Mesilate	Favipiravir + Nitazoxanide
		pyronaridine/artesunate) daily for 3 days Weight ≥65 kg: 4 tablets (720/240 mg pyronaridine/artesunate) daily for 3 days • Favipiravir + Nitazoxanide arm: 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 • Sofosbuvir + Daclatasvir arm: SOC plus sofosbuvir/daclatasvir (SOF/DCV) 1 tablet (400 mg/60 mg sofosbuvir/daclatasvir) daily for 7 days
Comparator (drug name and dosage)	• Favipiravir & standard treatment not further specified	• SOC arm: paracetamol, 2 tablets (1000 mg) to be taken 6-hourly as needed
Duration of observation/ Follow-up	Not described	Up to day 28
Primary Outcomes	• Time to alleviation of body temperature • Time to alleviation of SpO2 • Time to alleviation of chest image findings • time to SARS-CoV-2 PCR turn negative	• Incidence of SARS-CoV-2 clearance [Time Frame: Day 7]: proportion of participants with a negative nasal swab
Results/Publication	None, status 13 Nov. 2020	None, status 13 Nov. 2020

Table 4-24 Ongoing trial of combination therapies including Favipiravir and other substances: Azithromycin

Active substance	Favipiravir & Azithromycin
Sponsor	Ina-Respond, Indonesia
Trial Identifier	ClinicalTrials.gov Identifier: NCT04613271 Other Study ID Numbers: FVR
Phase & Intention	Phase 3, treatment Title: Phase III, Random-Open, Clinical Trials on the Efficacy and Safety of Favipiravir in Covid-19 Patients in Indonesia
Study design	Multicenter two-arm open label randomized controlled trial with parallel group assignment
Status of trial	Recruiting (last update at registry on 3 Nov. 2020)
Duration/End of Study	31 December 2020 (planned)
Study details	
Number of Patients	210
Disease severity	mild-moderate COVID-19 patients
Setting	Hospital
Location/Centres	3 hospitals in Indonesia
Intervention 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.
Comparator (drug name and dosage)	Azithromycin 500 mg once a day for 5 days.

Active substance	**Favipiravir & Azithromycin**
Duration of observation/ Follow-up	Up to 19 days of follow-up
Primary Outcomes	• Clinical improvement measured by no sign & symptom for 3 days and RT PCR negative
Results/Publication	None, status 9 Nov. 2020

For abbreviations see “List of abbreviations” at page 5.

5 REFERENCES

1. Khamis F, Al-Naabi H, Al-Lawati A, Ambusaidi Z, Al-Sharji M, Al-Barwani U, et al. Randomized Controlled Open Label Trial on the Use of Favipiravir Combined with Inhaled Interferon beta-1b in Hospitalized

Patients with Moderate to Severe COVID-19 Pneumonia. International Journal of Infectious Diseases 2020:Journal pre-print.

2. Yamamura H, Matsuura H, Nakagawa J, Fukuoka H, Domi H, Chujoh S. Effect of favipiravir and an anti-inflammatory strategy for COVID-19. Crit Care. 2020.

3. Doi K, Ikeda M, Hayase N, Moriya K, Morimura N. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series. Crit Care. 2020.

4. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: http://www.training.cochrane.org/handbook.

5. DerSimonian R LN. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

6. Balshem H HM, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology 2011;64:401-6.

7. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–53.

8. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11.

9. Siddiqui AJ, Jahan S, Ashraf SA, Alreshidi M, Ashraf MS, Patel M, et al. Current status and strategic possibilities on potential use of combinational drug therapy against COVID-19 caused by SARS-CoV-2. J Biomol Struct Dyn. 2020.

10. Remport A, Gerlei Z, Cseprekal O, Wagner L, Foldes K, Marton A, et al. Guidance on the special care of liver or kidney transplant recipients diagnosed with COVID-19. Orv Hetil. 2020.

11. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial: medRXiv; 2020 [Accessed 13 November 2020]. Available from: https://doi.org/10.1101/2020.03.17.20037432.

12. Lou Y, Liu L, Qiu Y. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial.

13. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clin Infect Dis. 2020.

14. Dabbous HM, El-Sayed MH, El Assal G, Elghazaly H, Ebeid FF, Sherief AF, et al. A randomized controlled study of favipiravir vs hydroxychloroquine In COVID-19 management: what have we learned so far. 2020 Accessed at 14-10-2020. Available from:

https://assets.researchsquare.com/files/rs-83677/v1/dc911adc-7762-41b9-adfe-0613bf7fcaed.pdf.

15. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19. Antimicrob Agents Chemother 2020;AAC.01897-20. Epub ahead of print.

16. jRCTs041190120. Multicenter, open-label, randomized trial of favipiravir in asymptomatic and minimally symptomatic patients infected with SARS-CoV2 to evaluate viral load reduction2020; Accessed at 14 September 2020. Available from: https://jrct.niph.go.jp/en-latest-detail/jRCTs041190120.

17. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020.

18. Calik BaSaran N, UyaroGlu OA, TelII Dizman G, OziSik L, SahIn TK, TaS Z, et al. Outcome of Non-Critical COVID-19 Patients with Early Hospitalization and Early Antiviral Treatment Outside the ICU. Turk J Med Sci. 2020.

19. Doi Y, Kondo M, Matsuyama A, Ando M, Kawatsuka Y, Ishihara T. Preliminary Report of the Favipiravir Observational Study in Japan (2020/5/15): Favipiravir Observational Study Group. 2020 Accessed: 10 September 2020. Available from: http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf.

20. Lou Y, Liu L, Yao H, Xingjiang H, Junwei S, Kaijin X, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. medRxiv [Internet]. 2020. Available from: doi: https://doi.org/10.1101/2020.04.29.20085761.

21. Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, et al. Should Favipiravir vs standard treatment be used for COVID-19? Italy: Department of Epidemiology Lazio Regional Health Service (DEPLazio); 2020 [Available from: http://deplazio.net/farmacicovid/index.html.

22. Chen C, Huang J, Cheng Z, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv 2020 [Internet]. 2020. Available from: https://doi.org/10.1101/2020.03.17.20037432.

23. Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, et al. Should Favipiravir vs Umifenovir be used for COVID-19? Italy: Department of Epidemiology Lazio Regional Health Service (DEPLazio); 2020 [Available from: http://deplazio.net/farmacicovid/index.html.

24. NCT04542694. Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19.

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])	06/11/2020

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"	06/11/2020
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"	06/11/2020
Citation screening	-	Citation screening of all systematic reviews evaluating favipiravir, identified in NIH LitCovid and NIPH (n=17 systematic reviews)	10/09/'20
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 (1 RCT with outcome data)	13/11/'20
PubMed	pubmed.ncbi.nlm.nih.gov	Performed on all identified ongoing studies: PubMed search using trial registry ID or acronym as search terms (1 RCT with outcome data)	13/11/'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. We receive studies that EPPI Centre has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 15 included COVID-19 drugs.

Table 6-2 depicts the search strategy executed by NIPHNO up to 27 September 2020 and the search strategy by SNHTA up to 10 September 2020.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
Search strategy as executed by NIPHNO for version 4 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	27/09/'20 until 25/10/'20	378
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. 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	27/09/'20 until 25/10/'20	

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
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	27/09/'20 until 25/10/'20	
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)	27/09/'20 until 25/10/'20	
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

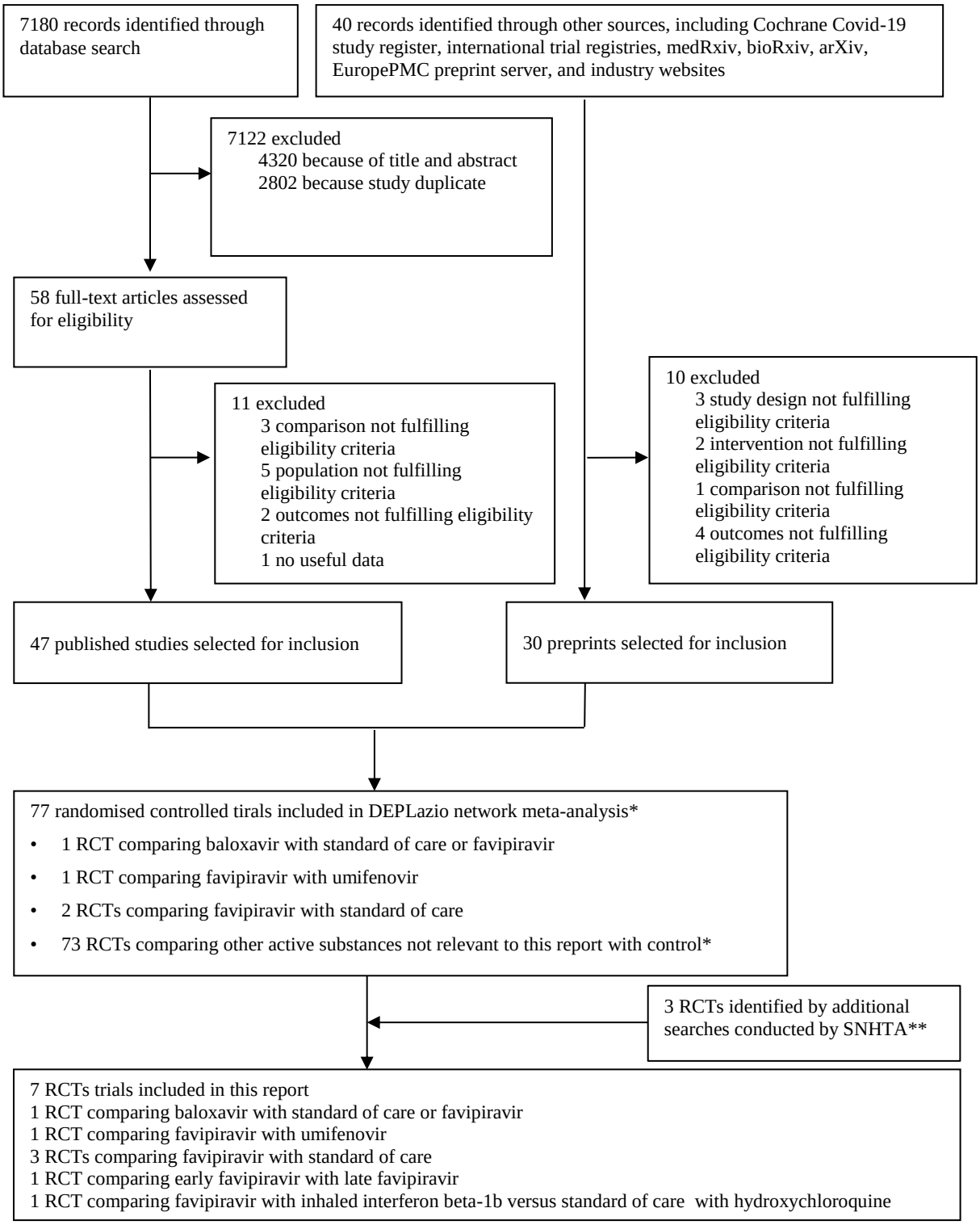
SNHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and favipiravir are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
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	13/ 11/'20	40 3 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 The same intervention terms were combined with the term «SARS»	13/11/'20	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	13/11/'20	8 0 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 4 identified trials are considered in the summary of findings tables in this report. ** three recently identified trials with outcome data were 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. These will be considered in the summary of findings tables in the next version of this report.

Table 6-4 Summary of effectiveness and safety from recently identified RCTs of Favipiravir not yet included in summary of findings tables

Author, year	NCT04542694 [24]	Khamis 2020 [1]
Country	Russia	Oman
Sponsor	Promomed, LLC	Royal Hospital, Muscat, Oman
Intervention/Product (drug name)	Favipiravir (areplivir)	Favipiravir plus inhaled Interferon beta-1b
Dosage	Favipiravir (Areplivir): 1600 mg (8 tablets) BID on day 1; 600 mg (3 tablets) BID on day 2-14.	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)
Comparator	Standard of care (SoC): 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. Might include hydroxychloroquine (with or without azithromycin), chloroquine, lopinavir/ritonavir or other recommended schemes.	SoC: based on the national guidelines that had HCQ 400 mg bid on day 1, 200 mg BID on day 2 to 7
Study design	Multicenter, 2-arm randomized open label controlled trial with parallel group assignment.	2-arm randomized open label controlled trial with parallel group assignment.
Setting	Hospitalized	Hospitalised
Number of pts	200	98
Age of patients (yrs)	Mean (SD): 49.7 (13.1)	Mean (SD): 55 (14)
Disease severity	Mild to moderate	Moderate to severe
Follow-up (months)	Up to 28 days	Up to 15 days
Loss to follow-up, n (%)	None reported, 4 / 100 in the FV group and 0 / 100 in the SoC group did not complete the treatment	None reported
SOF eligible outcome data		
SARS-CoV-2 clearance	Negative PCR by day 10 98 / 100 in the FV group 79 / 100 in the SoC group. Difference in percentage: 22.5% (P=0.00016 from Chi-Squared test)	-
Number of patients with respiratory failure and respiratory distress syndrome	-	-
All-cause mortality	0 / 100 (0%) in the FV group 0 / 100 (0%) in the SoC group	6 / 45 (13.3%) in the FV based group 5 / 44 (11.4%) in the SoC group
Number of patients discharged at day 15	-	31 / 45 (68.9%) in the FV based group 29 / 44 (65.9%) in the SoC group
Improvement in lung disease on CT	60 / 100 (60%) in the FV group 40 / 100 (40%) in the SoC group P value from Chi-squared test reported as 0.195; type of analyses and timepoint unclear, as three time-points(15, 21 and 28 days) were measured.	-
Serious AE (SAE), n (%)	3/100 (30%) in the FV group: one with an aortic valve stenosis, one with multiple organ failure syndrome and one with respiratory failure. 0/100 (0%) in the SoC group	-
Overall AEs, n (%)	-	-
Other effectiveness outcomes		
non-invasive or mechanical ventilation	Up to 28 days 0 / 100 (0%) in the FV group 0 / 100 (0%) in the SoC group	-

Author, year	NCT04542694 [24]	Khamis 2020 [1]
Admission to ICU	Up to 28 days 0 / 100 (0%) in the FV group 0 / 100 (0%) in the SoC group	8 / 45 (17.8%) in the FV based group 8 / 44 (18.2%) in the SoC group
Clinical improvement	Improvement of 2 or more categories on the WHO ordinal scale for clinical improvement (WHO-OSCI) by day 10. Higher scores indicate worse outcome. 27 / 100 (27%) in the FV group 15 / 100 (15) in the SoC group Difference in proportions: 13% (95% CI 0.0% to 23.7%; p = 0.037) Time before end of fever, defined time in days with body temperature below 37.2 degrees Celsius for three consecutive days without antipyretic medication 4 days (IQR 2 to 5) in the FV group 5 days (IQR 3 to 7) in the SoC group (P=0.052 from Log Rank test) Post-hoc outcome: patients without any clinical signs of disease by the completion of therapy at day 10 (category 0 according to a WHO Categorical Ordinal Scale) 44 / 100 (44%) in the favipiravir group 10 / 100 (10%) in the SoC group Post-hoc outcome: number of patients achieving a category lower than or equal to 2 on the WHO clinical improvement scale by day 10: 90 / 100 (90%) in the FV group 67 / 100 (67%) in the SoC group	-
Time to clinical improvement	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	-
Length of Stay in hospital	-	Median (IQR): 7 (3-11) in FV based group Median (IQR): 7 (4-12) in SoC group
Other safety outcomes		
Most frequent AEs n (%)	-	**-**
Most frequent SAEs, n (%)	-	-
AEs of special interest, n (%)	Increased alanine or aspartate aminotransferase activity: 25 / 100 (25%) patients in the FV group 28 / 100 (28%) in the SoC group	-
Death as SAE, n (%)	0 / 100 (0%) in the FV group 0 / 100 (0%) in the SoC group	-
Withdrawals due AEs, n (%)	1 / 100 (1%) in the FV group 0 / 100 (0%) in the SoC group	-

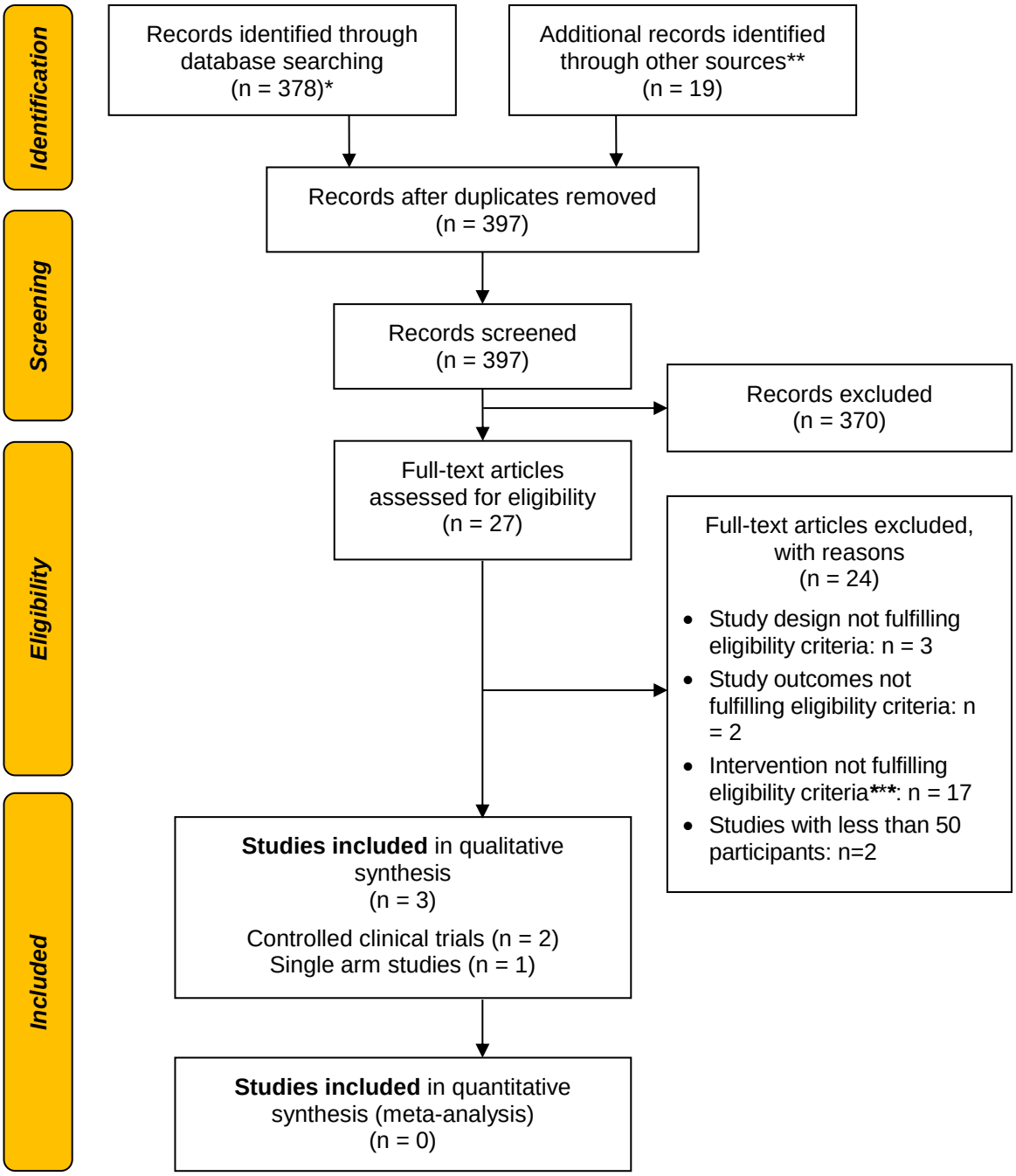
Abbreviations: FV = favipiravir; BID = twice daily; ICU = intensive care unit; SoC = standard of care
In NCT04542694, all patients randomised contributed to all analyses.

Table 6-5 Summary of effectiveness and safety from recently identified RCTs of Favipiravir not yet included in summary of findings tables

Author, year	JPRN-jRCTs041190120 [15, 16]
Country	Japan
Sponsor	Fujita Medical University Hospital
Intervention/Product (drug name)	Favipiravir (avigan)
Dosage	Early treatment with Favipiravir: immediate treatment with favipiravir on day 1

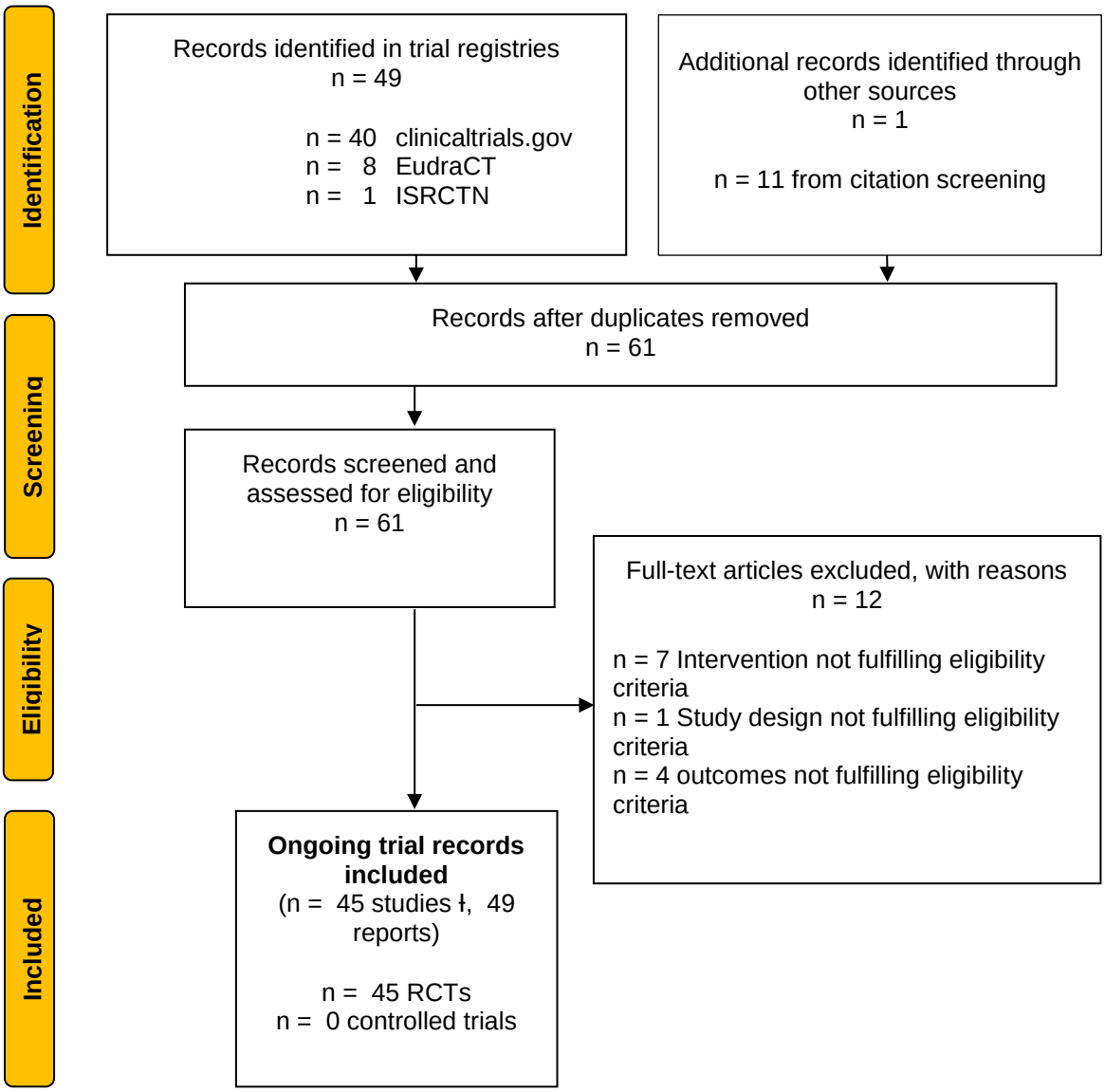
Author, year	JPRN-jRCTs041190120 [15, 16]
Comparator	Late treatment with Favipiravir: delayed treatment with favipiravir on day 6
Study design	Multicenter, open-label, randomized clinical trial (phase-2)
Setting	Outpatients
Number of pts	89
Age of patients (yrs)	Median: 50 years
Disease severity	asymptomatic and mildly ill patients with SARS-CoV2 infection
Follow-up (months)	Up to 10 days
Loss to follow-up, n (%)	Unclear, 1 withdrew consent, 82 out of 89 randomised are included in the safety analyses.
SOF eligible outcome data	
SARS-CoV-2 clearance	By day 10 86.1% in the early FV group 83.1% in the late FV group Adjusted hazard ratio [aHR] of 1.27; 95% confidence interval [95% CI], 0.74–2.1). By day 6 66.7% in the early FV group 56.1% in the late FV group Adjusted hazard ratio [aHR] of 1.42; 95% confidence interval [95% CI], 0.76–2.62). 50% reduction in SARS- CoV2 copy number: 94.4% in the early FV group 78.8% of the late FV group (adjusted odds ratio, 4.75; 95% CI, 0.88-25.76; P=0.071). “Changes in SARS-CoV2 copy number on a logarithmic scale did not reach statistical significance over time.”
Number of patients with respiratory failure and respiratory distress syndrome	-
All-cause mortality	28 to 91 days: 0 / (0%) in the early FV group 0 / (0%) in the late FV group
Number of patients discharged at day 15	-
Improvement in lung disease on CT	-
Serious AE (SAE), n (%)	-
Overall AEs, n (%)	Safety data was reported across both groups, not allowing the calculation or relative estimates. A total of 144 adverse events were reported among the 82 patients in the safety population, consisting of patients who received at least one dose of favpiravir.
Other effectiveness outcomes	
non-invasive or mechanical ventilation	-
Admission to ICU	-
Clinical improvement	“Neither disease progression nor death occurred to any of the patients in either treatment group during the 28-91 day participation.” Of 30 patients who had a fever (≥37.5°C) on day 1, time to defervescence was 2.1 days and 3.2 days in the early and late treatment groups (aHR, 1.88; 95%CI, 0.81–4.35).
Time to clinical improvement	-
Length of Stay in hospital	-
Other safety outcomes	
Most frequent AEs n (%)	Transient hyperuricemia, occurring in 69 out of 82 patients (84.1%). Data not reported by group.
Most frequent SAEs, n (%)	-
AEs of special interest, n (%)	-
Death as SAE, n (%)	-
Withdrawals due AEs, n (%)	-

Abbreviations: FV = favipiravir; BID = twice daily; ICU = intensive care unit; SoC = standard of care; JPRN-jRCT = Japan Register of Clinical Trials (JRCT) identifier



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies

* Hits from searches executed by NIPHNO in the period 27 September 2020 to 25 October 2020;
** including five studies identified in previous versions of this report, see previous versions of this report.
*** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews



Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies

** *ongoing studies identified in systematic reviews;* ł *four added in this update;* ǂ *described in* Table 4-4*; RCT = randomised controlled trial*