EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

FAVIPIRAVIR FOR THE TREATMENT OF COVID-19

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Monitoring Report

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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	**18/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
Methods, p. 8	The description of the search methods for observational and ongoing studies is expanded: • Search methods are described in Appendix Tables 1-2 • A flow diagram was added
p. 22 ff.	The structure of the tables describing ongoing studies has changed: • at outcome, we now focus on the description of primary outcomes • we no longer list trial collaborators
	The pool of included studies has changed. The following were added: • One completed RCT in the summary of findings tables [1]. • One completed observational study [2]. • Eleven ongoing studies evaluating favipiravir as single agent (IRCT20151227025726N14, JPRN-JapicCTI-205238, EudraCT 2020-001528-32, NCT04529499, NCT04542694, ChiCTR2000029548, ChiCTR2000030113, ChiCTR2000029996, JPRN-jRCTs041190120, ChiCTR2000030254, TCTR20200514001) • Four ongoing studies evaluating favipiravir as part of a combination therapy (IRCT20200318046812N1, jRCTs031200026, IRCT20200428047228N1, NCT04532931) The following are pending inclusion • Two ongoing RCTs are pending inclusion, as the Clinical Trials Registry-India was offline at time of the drafting of this report (IDs CTRI/2020/05/025114 & CTRI/2020/06/025957).
	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.

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Conflict of interest

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

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
AZ	azithromycin
BID	Twice daily
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
FV	favipiravir
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HQ	hydroxychloroquine
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
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.

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.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [3].

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

- 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/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

Search methods are described in more detail in Appendix Table 1.

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	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. The screening process is depicted in a flow diagram [6]. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

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/

Search methods are described in more detail in Appendix Table 2.

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies. The process of study selection is depicted in the a flow diagram.

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 [7].

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 [8, 9].

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 diagram (Figure 1) depicts the screening process to identify eligible studies.

Two RCTs have been published evaluating favipiravir in Chinese population [10, 11]. 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 [11]. 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) [10]. 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 this update [1]. The trial compared two dosing shedules 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.

One RCT with Japan Register of Clinical Trials (JRCT) number JPRN-jRCTs041190120 was completed on June 15 2020 and summary outcome data has been uploaded to the registration site recently [12]. This multicenter, open-label, randomized clinical trial evaluated immediate treatment with favipiravir (avigan) on day 1 with a delayed scheme on day 6. Eighty-nine asymptomatic and mildly ill patients with SARS-CoV2 infection were included. Outcome data of this trial may be considered for inclusion in the next update of this report.

In this update, we also identified one large prospective uncontrolled observational study explicitly reporting to evaluate avigan [2]. 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. **Fehler! Verweisquelle konnte nicht gefunden werden.** describes the Japanese and four additional non-randomised observational studies that reported safety outcomes for Favipiravir of any brandname [2, 13-16]. One study had a 3-arm comparative design evaluating favipiravir with hydroxychloroquine (HQ) with or without azithromycin (AZ). One study had a controlled before-after design comparing favipiravir with Lopinavir/ritonavir. Two studies were cases series that seemed prospective. 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

The two 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, so that we did not provide comparative data for this outcome in our Summary of Findings Table. The certainty of the evidence was very low for all other outcomes of interest to this report. Favipiravir compared to standard care may lead to fewer patient with viral clearance, may lead to an increased number of patients with respiratory failure and respiratory distress syndrome, may lead to a decreased number of patients discharged at day 15, may lead to an improvement in lung disease on CTX, may increase the number of patients with serious adverse events and may increase the number of patients with adverse events importantly, but the evidence is very uncertain. 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.

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 [17]. 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%) [2]. 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 4-17 describe ongoing trials for favipiravir of any brandname.

In this update, we added 15 ongoing studies, so that 39 ongoing studies are included in total. Of these, 11 evaluate favipiravir in combination with another pharmacotherapy in Covid-19 patients, 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 [1] is included in these tables. Two randomised ongoing trials are pending inclusion, as the Clinical Trials Registry-India (CTRI) was offline at the time this report was compiled. The trial with identifier CTRI/2020/06/025957 seems to evaluate favipiravir versus standard of care in 150 adults with mild-to-moderate COVID-19. The trial with identifier CTRI/2020/05/025114 seems to evaluate the addition of Umifenovir to favipiravir versus favipiravir alone in 158 patients with Covid-19 in India.

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.

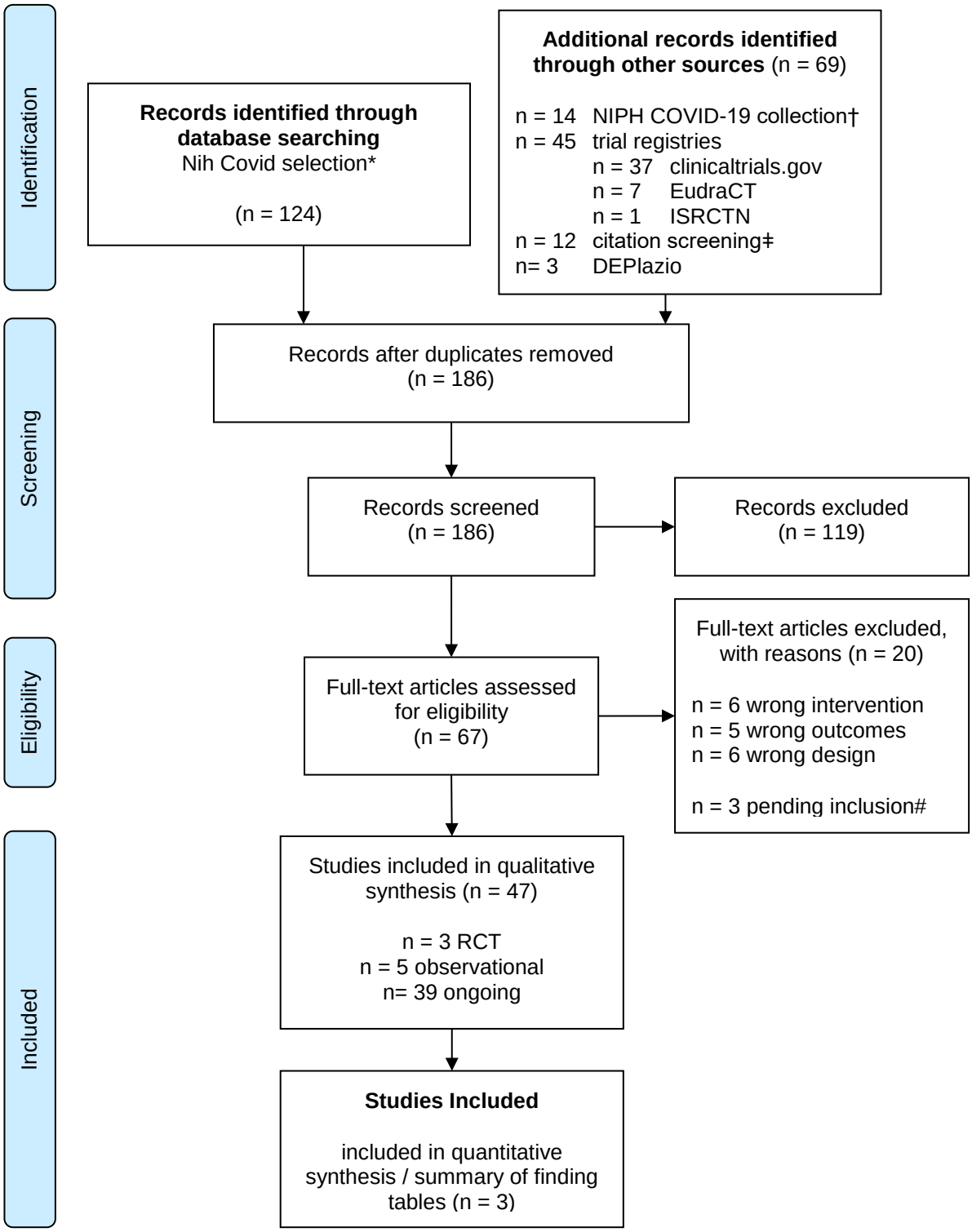

Figure 1: Flow Diagram

* from https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info; † from www.nornesk.no/forskningskart/NIPH_interventionsTreatMap.html; ǂ citation screening of 17 systematic reviews; # 1 completed and 2 ongoing RCTs; DEPLazio = department of Epidemiology Lazio Regional Health Service, Italy. Systematic search by DEPlazio is described elsewhere; RCT = randomised controlled trial

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	933 per 1000	868 per 1000 (700 to 1000)	RR 0.93 (0.75 to 1.16)	59 (2[b]) [1, 18]	very low[c,d]	65 fewer per 1.000 (from 233 fewer to 149 more)
Number of patients with respiratory failure and respiratory distress syndrome	400 per 1000	444 per 1000 (451 to 944)	RR 1.11 (0.39 to 3.19)	19 (1) [18]	very low[d,e]	44 more per 1.000 (from 244 fewer to 876 more)
All-cause mortality				59 (2[b]) [1, 18]	very low[c,f]	No death occurred during the study period in the study of Lou et al. Two patients on AVIFAVIR 1600/600 mg died in the trial by Ivashchenko et al.
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) [1]	very low[f,h]	204 fewer per 1.000 (from 399 fewer to 94 more)
Improvement in lung disease on CT	800 per 1000	904 per 1000 (688 to 1000)	RR 1.13 (0.86 to 1.46)	40 (1) [1]	very low[f,g]	104 more per 1000 (from 112 fewer to 368 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) [1]	very low[e,f]	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) [1]	very low[f,g]	250 more per 1000 (from 43 fewer to 952 more)

Source: publication by Lou et al, 2020 [11], related to Chinese Clinical Trial Registry ID: ChiCTR2000029544; publication by Ivashchenko et al, 2020 [1]: Clinicaltrias.gov ID: NCT04434248). Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [19], 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. 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.
b. In the Ivashchenko study we considered the group Favipiravir 1600/600mg
c. Downgraded two levels for high risk of performance bias and unclear risk of selection bias in both studies and reporting bias at high risk in one study and unclear in the other
d. Downgraded two levels for very low number of events and very small sample size
e. Downgraded two levels for high risk of performance bias and unclear risk of selection bias and reporting bias
f. Downgraded two levels for very small sample size
g. Downgraded of two levels for high risk of performance and reporting bias and unclear risk of selection bias

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 [10], related to Chinese Clinical Trial Registry ID ChiCTR200030254. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [20], 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]	Doi 2020 [12]	Yamamura 2020 [13]	Calik 2020 [11]
Country	China	Japan	Japan	Turkey
Sponsor	The Third People's Hospital of Shenzhen	Not described	Not described	Not described
Intervention/Product (drug name)	Favipiravir (FV) by Zhejiang Hisun Pharmaceutical Co., LTD) & interferon-alpha	Favipiravir (not described)	Favipiravir (not described), methylprednisolone, heparin	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	3600 mg total on day 1; 1600 mg total on day 2 to median of 14 days	Favipiravir: 3600 mg total on day 1; 1600 mg total on day 2 to median of 14 days Methylprednisolone: 1000 mg for 3 days Dexmedetomidine, dose not reported Unfractionated heparin:10000 to 12000 IU/day or LMWH 2000 IU bid	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.)	Case series, likely prospective	Prospective case serires	Prospective observational single center study
Setting	Hospital	Hospitalised at ICU	Hospitalised	Hospitalised
Number of pts	Overall: 80 Experimental: 35 Control: 45	11	13	174 168 described FV: 32 HQ: 23 HQ-AZ: 113

Author, year	Cai 2020 [16]	Doi 2020 [12]	Yamamura 2020 [13]	Calik 2020 [11]
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.	Eleven adults with reverse transcriptase polymerase chain reaction-confirmed SARS-CoV-2 infection	All patients transferred from other hospitals who required mechanical ventilation for severe COVID-19	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)†	68 (median)	63	45.5 (median)
Disease severity	Nonsevere COVID-19	Critical	Severe	Mild to Severe
Follow-up (months)	Up to 14 days	Minimum 33 days of hospital follow-up	Not described, likely up to 17 days	Not described, median hospitalisation 4 days (0 to 28 days)
Loss to follow-up, n (%)	0 (0%)	Not described	Not described	Not described
RoB	High RoB Very low-quality evidence	-#	-#	High RoB Very low-quality evidence
Safety – Outcomes*				
Overall AEs, n (%)	FV: 4 / 35 (11.43%) L/R: 25 / 45 (55.56%)	-	-	-
Serious AE (SAE), n (%)	-	-	-	-

Author, year	Cai 2020 [16]	Doi 2020 [12]	Yamamura 2020 [13]	Calik 2020 [11]
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 (%)	-	-	1 (7.7%) ǂ	-
Withdrawals due AEs, n (%)	FV: (0%) L/R: (0.0%))	1 (9.1%)	-	FV: 0 (0%) HQ: 0 (0%) HQ-AZ: 0 (0%)

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

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

Author, year	Doi 2020
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

Author, year	Doi 2020
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 14 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 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	None, status 14 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 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 14 Sept. 20	None, status 10 Sept. 2020	None, status 10 Sept. 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 27 August June 2020)	Completed (last update at registry on 11 Sept. 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 sustained clinical recovery (Stage 1) [Time Frame: 1-28 days]: the earliest time point at which ○ Patient is maintaining blood oxygen saturation >93% on room air at sea level, AND ○ ALL COVID-19 associated symptoms (fever, chills, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms-specifically diarrhoea and vomiting, shortness of breath or dyspnoea) reported in the patient have reached a severity of "0 - absent" or "1 - mild"* in assessments over a continuous period of 48 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 10 Sept. 2020	None, status 14 Sept. 2020	None, status 14 Sept. 2020

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

Table 4-9. Ongoing phase 2 trials of single agents: Favipiravir

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 9	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: CONTROLCOVIDFavipiravir-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 14 Sept. 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	Avigan/ Favipiravir: 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 9 tablets by mouth twice daily for one day, followed by 4 tablets twice daily (Maximum days of therapy is 7 days)	None	Placebo: 8 tablets orally twice daily on day 1, followed by 4 tablets twice daily from days 2-25. The dosage of favipiravir placebo for treatment is 10 tablets orally twice daily on day 1, followed by tablets twice daily from days 2-14
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 10 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 20

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

Table 4-10 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 9 Sept. 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 10 Sept. 20	None, status 14 Sept. 20	Interim report published [1], status 14 Sept. 20

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

Table 4-11 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: Oral Favipiravir Compared to Placebo in Subjects With Mild 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 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 27 July. 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 14 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 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	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 (status 7 Sept. 20)	Ongoing, not yet recruiting* (last update at trial registry 5 Aug. 2020)
Duration/End of Study	May 2020 (planned end of study)	May 2021	From 17 August 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 14 Sept. 20	None, status 10 Sept. 20	None, status 14 Sept. 20

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	Peking University First Hospital	Tanta University	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	ClinicalTrials.gov Identifier: NCT04345419
Phase & Intention	Not described, treatment Title: Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive	Phase 2/3, treatment Title: Efficacy of Faviprevir in COVID-19 Treatment	Phase 2/3, treatment Title: A Real-life Experience on Treatment of Patients With COVID 1
Study design	Multicenter randomized open label controlled trial with parallel group assignment	Multicenter randomized open label controlled trial with parallel group assignment	Multicenter randomized single blinded controlled trial with parallel group assignment

Status of trial	Recruiting (last update at trial registry: 24 April 2020)	Recruiting (last update at trial registry: 19 August 2020)	Recruiting (last update at trial registry: 18 August 2020)
Duration/End of Study	15 September 2020 (planned end of study)	December 1, 2030	December 2029
Study details			
Number of Patients	210	40	120
Disease severity	Not described	Not described	Not described
Setting	Not described	Not described	Not described
Location/Centres	China, 8 centers in Anhui, Hubei and Zhejiang	Egypt, Tanta, 1 center listed	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	Faviprevir, not further described
Comparator (drug name and dosage)	Regular treatment group	Placebo	• Chloroquine pills (Alexoquine) • Nitazoxanide • (alenia;nanazoxid) • Ivermectin (ivactin) • Yomesan or niclosamide tablets (Yomean, Niclosamide) • Other drugs as oseltamivir or combination of any of the above treatment
Duration of observation/ Follow-up	Up to 5 months	Up to 6 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 viral cure [Time Frame: 6 months]	Primary efficacy outcome: • Number of patients with decreased viral load [Time Frame: 6 months]
Results/Publication	None, status 14 Sept. 20	None, status 10 Sept. 20	None, status 14 Sept. 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	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 10 Sept. 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 4-15 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)	None, status 10 Sept. 2020	None, status 10 Sept. 2020

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

Table 4-16 Ongoing trials of combination therapies including Favipiravir

Active substance	**Favipiravir (Avigan) and + Kaletra (Lopinavir/ritonavir)**	**Favipiravir and Hydroxychloroquine**	**Favipiravir and Hydroxychloroquine**
Sponsor	University College London Comprehensive Clinical Trial Unit, UK	King Abdullah International Medical Research Center	Shahid Beheshti University of Medical Sciences
Trial Identifier	EudraCT number: 2020-002106-68 ClinicalTrials.gov Identifier: NCT04499677 Trial acronym: FLARE - Favipiravir +/- Lopinavir: A RCT of Early Antivirals	ClinicalTrial.gov: NCT04392973 Trial acronym: FACCT - FAvipiravir and HydroxyChloroquine Combination Therapy Other Study ID Numbers: RC20/174	NCT04359615 Trial acronym: FIC
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	Phase not described, Treatment Title: A Trial of Favipiravir and Hydroxychloroquine Combination in Adults Hospitalized With Moderate and Severe Covid-19	Phase 3 (described by trial authors as phase 4) Title: Favipiravir in Hospitalized COVID-19 Patients
Study design	Multicenter, randomised, double-blind, 2x2 factorial placebo-controlled trial Masking: triple (participant, care provider, investigator)	Multicenter, open label, randomised controlled trial in parallel design	Single center 2-arm randomised triple blinded controlled trial with parallel group design
Status of trial	Not yet recruiting (last update at trial registry 5 Aug. 2020*)	Recruiting (last update at trial registry 28 July 2020)	Not yet recruiting (last update at trial registry 28 April 2020)
Duration/End of Study	From 17 August 2020 to 1 March 2021	From 21 may 2020 to November 2021	From 20 April 2020 to 5 May 2020 (planned)
Study details			
Number of Patients	240	520	40
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	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
Setting	Not described, likely outpatients	Hospitalised	Hospitalized
Location/Centres	UK, 4 sites	Saudi Arabia, 8 sites	Iran, Tehran 1 center
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	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	Favipirair & Hydroxychloroquine, dose and route of administration not reported

Active substance	Favipiravir (Avigan) and + Kaletra (Lopinavir/ritonavir)	Favipiravir and Hydroxychloroquine	Favipiravir and Hydroxychloroquine
	Trial arm with single agent: Kaletra (Lopinavir/ritonavir), 200/50 mg daily, oral intake	+ 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.	
Comparator (drug name and dosage)	Matched Placebo, oral intake, dosing scheme and mg identical to Avigan and Kaletra schemes.*	Standard of care	Hydroxychloroquine, dose and route of administration not reported
Duration of observation/ Follow-up	Up to 28 days of follow-up	Up to 28 days of follow-up	Up to 14 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	• clinical improvement up to 28 days, defined as the time from the randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live discharge from the hospital, whichever came first.	•Time to clinical improvement up to 14 days
Results/Publication	None, status 14 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 20

Table 4-17 Ongoing trials of combination therapies including Favipiravir, continued

Active substance	Maraviroc+Favipiravir+ Currently used therapy	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine	Favipiravir Combined With Tocilizumab	Favipiravir/Hydroxychloroquine
Sponsor	Hospital General de México Dr. Eduardo Liceaga	Rajavithi Hospital	Peking University First Hospital	Baqiyatallah Medical Sciences University
Trial Identifier	ClinicalTrials.gov Identifier: NCT04475991 Acronym: COMVIVIR	ClinicalTrials.gov Identifier: NCT04303299 Acronym: previously THDMS-COVID-19; currently fight COVID-19	ClinicalTrials.gov Identifier: NCT04310228 Chinese Clinical Trial Registry ID: ChiCTR2000030894 Other study ID: 2020YFC0844100	ClinicalTrials.gov Identifier: NCT04376814
Phase & Intention	Phase 2, treatment Title: Safety and Efficacy of Maraviroc and/or Favipiravir vs Currently Used Therapy in Severe COVID-19 Adults	Phase 3, treatment Title (new title): Favipiravir, Protease Inhibitors, Oseltamivir - Gpo, Hydroxychloroquine for Treatment of COVID-19 (FIGHT-COVID-19)	Phase not described, treatment Title: Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	Phase not described, treatment Short title: Favipiravir Plus Hydroxychloroquine and Lopinavir/Ritonavir Plus Hydroxychloroquine in COVID-19
Study design	Randomized open label controlled trial with parallel group assignment	Open label eight-arm randomised controlled study with parallel group design.	Multicenter 3-arm randomized open label controlled trial with parallel group assignment	Non-randomized open label controlled trial with parallel group assignment

Active substance	Maraviroc+Favipiravir+ Currently used therapy	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine	Favipiravir Combined With Tocilizumab	Favipiravir/Hydroxychloroquine
		PROBE design - prospective randomised open blinded evaluation). Outcome assessors are masked for allocation status.		
Status of trial	Not yet recruiting (last update at trial registry 2 Sept. 2020)	Recruiting (last update at trial registry 1 Sept. 2020)	Recruiting (last update at trial registry 10 April 2020)	Completed (last update at trial registry 16 June 2020)
Duration/End of Study	January 2021	31 December 2021	May 2020 (planned end of study)	May 25, 2020 (actual)
Study details				
Number of Patients	100	320	150	40
Disease severity	Severe COVID-19	Mild to critical COVID-19	Likely mild to moderate, excluded who required hospitalization	Not described, requiring hospitalization
Setting	Inpatients	In- and outpatients	outpatients	Inpatients
Location/Centres	Mexico, Mexico City	Thailand, Bangkok	China, 6 centers in Beijing and Hubei	Iran, Tehran
Intervention drug name and dosage	• 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).	• 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	• 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	• 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)	• Maraviroc + Currently used therapy: Maraviroc tablets. 300	• Oseltamivir plus Chloroquine in Mild COVID19: Oseltamivir	• Tocilizumab group: the first dose is 4 ~ 8 mg/kg and the	• Hydroxychloroquine 400mg tablets two times per day

Active substance	Maraviroc+Favipiravir+ Currently used therapy	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine	Favipiravir Combined With Tocilizumab	Favipiravir/Hydroxychloroquine
	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"	300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 800 mg per day In mild COVID19 • Darunavir and Ritonavir plus oseltamivir: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus plus Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 400mg per day in Mild COVID19 • Lopinavir and Ritonavir plus Oseltamivir in mild COVID19: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In mild COVID19 • Lopinavir and Ritonavir Oseltamivir moderate to severe COVID19: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In moderate to critically ill COVID19 • Darunavir /ritonavir oseltamivir chloroquine mod-severe: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19 • Conventional Quarantine: “Patient who unwilling to	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.	• 200/50 mg of Lopinavir / Ritonavir (Kaletra) two times per day for seven days

Active substance	Maraviroc+Favipiravir+ Currently used therapy	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine	Favipiravir Combined With Tocilizumab	Favipiravir/Hydroxychloroquine
		treatment and willing to quarantine in mild COVID19"		
Duration of observation/ Follow-up	Up to 28 days	Up to 24 weeks	Up to 3 months	Up to 28 days
Primary Outcomes	• Patients free of mechanical ventilation or death [Time Frame: 28 days post start]	• SARS-CoV-2 eradication time [Time Frame: Up to 24 weeks]	• Clinical cure rate [Time Frame: 3 months]	• 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] • 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 10 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 20	None, status 14 Sept. 20

Table 4-18 Ongoing trials of combination therapies including Favipiravir, continued

Active substance	Favipiravir/Hydroxychloroquine	Favipiravir + Nafamostat Mesilate	favipiravir + hydroxychloroquine	Favipiravir + Nitazoxanide
Sponsor	Iran university of medical sciences Second sponsor: Bagheiat-allah University of Medical Sciences	Not reported, likely the University of Tokyo	Quality Improvement of Intensive Care Research Center- Shahid Beheshti University	Shin Poong Pharmaceutical Co. Ltd.
Trial Identifier	Iranean registry of Randomised Trials (IRCT) registration number: IRCT20200318046812N1	Japan Registry of Clinical Trials ID: jRCTs031200026	Iranean Registry of Randomised Trials (IRCT) registration number: IRCT20200428047228N1	ClinicalTrials.gov Identifier: NCT04532931 Other Study ID Numbers: SP-PA-COV-202
Phase & Intention	Treatment Phase 3	Treatment Phase not described	Treatment Phase 3	Treatment Phase 2

Active substance	Favipiravir/Hydroxychloroquine	Favipiravir + Nafamostat Mesilate	favipiravir + hydroxychloroquine	Favipiravir + Nitazoxanide
	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	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	Title: Evaluation of the efficiency and safety of favipiravir + hydroxychloroquine drug regimen in comparison with hydroxychloroquine in hospitalized patients with covid-19	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	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.	Multicenter, Single blinded Randomized Controlled, Comparative Study with parallel group assignment	Double blinded randomized controlled trial with parallel group assignment. Masking of participants, care providers & outcome assessors. Simple randomization using a Random Number Table	Randomized, adaptive, single center open label controlled trial with parallel group design.
Status of trial	Recruitment completed (last update at registry: 26 August 2020)	Recruiting (last update at registry: 28 August 2020)	Recruitment complete (last update at registry: 16 May 2020)	Recruiting (last update at registry: 7 Sept. 2020)
Duration/End of Study	Not reported	Not reported	Not reported	January 21 (planned end of study)
Study details				
Number of Patients	324	160	50	250
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	COVID-19 with pneumonia. Excluded are patients “having less than 93% of oxygen saturation (SpO2) in without the oxygen administration”	Not reported	Mild
Setting	Hospitalised	Likely hospitalised	Hospitalised	Outpatients
Location/Centres	Iran, 20 centers all over the country	Japan, Tokyo	Iran	South Africa, Johannesburg: single center
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	Favipiravir and Nafamostat Mesilate & standard treatment not further specified	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).	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

Active substance	Favipiravir/Hydroxychloroquine	Favipiravir + Nafamostat Mesilate	favipiravir + hydroxychloroquine	Favipiravir + Nitazoxanide
	according to clinical response of the patient. Other supportive and routine care will be the same in both groups.			• Pyronaridine + Artesunate arm: SOC plus pyronaridine-artesunate (PA) Weight 45 to <65 kg: 3 tablets (540/180 mg pyronaridine/artesunate) daily for 3 days Weight ≥65 kg: 4 tablets (720/240 mg pyronaridine/artesunate) daily for 3 days • 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)	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.	Favipiravir & standard treatment not further specified	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).	SOC arm: paracetamol, 2 tablets (1000 mg) to be taken 6-hourly as needed
Duration of observation/ Follow-up	Not described	Not described	Not described	Up to day 28
Primary Outcomes	• Admission to intensive care unit	• Time to alleviation of body temperature • Time to alleviation of SpO2 • Time to alleviation of chest image findings	• No fever for 3 days • SpO2>93% • CXR observation	• Incidence of SARS-CoV-2 clearance [Time Frame: Day 7]: proportion of participants with a negative nasal swab

Active substance	Favipiravir/Hydroxychloroquine	Favipiravir + Nafamostat Mesilate	favipiravir + hydroxychloroquine	Favipiravir + Nitazoxanide
		• time to SARS-CoV-2 PCR turn negative		
Results/Publication	None, status 10 Sept. 2020	None, status 10 Sept. 2020	None, status 10 Sept. 2020	None, status 14 Sept. 2020

5 APPENDIX

Appendix Table 1 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
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 August 2020	86
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 September 2020	124, including 86 previously identified
NIPH	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Seaching “Interventions to treat the infected patient” Ticking “Flavipiravir”, “Any population”	10 August 2020	12
NIPH	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Seaching “Interventions to treat the infected patient” Ticking “Flavipiravir”, “Any population”	10 September 2020	14, including 12 previously identified
Citation screening	-	Citation screening of all systematic reviews evaluating favipiravir, identified in NIH LitCovid and NIPH	10 September 2020	17 systematic reviews (1 observational study identified)

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

Appendix Table 2 Search strategy to identify ongoing studies

Database	URL	Search terms / Search modality	Hits retrieved	Date of search
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at Condition or disease: • covid-19 • SARS Terms used at “other terms”: • Favipiravir • Avigan • T-705 • T705	32	10 August 2020

Database	URL	Search terms / Search modality	Hits retrieved	Date of search
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 now automatically searched	36 including 31 from previous search	10 September 2020
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and Favipiravir • covid-19 and avigan • covid-19 and T-705 The same intervention terms were combined with the term «SARS», giving identical hits	Overall: 0 0 0 0	10 August 2020
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», giving identical hits	Overall: 1 1 0 0 0 0 0 0 0 0 0 0	10 September 2020
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and Favipiravir • SARS and favipiravir • covid-19 and avigan • SARS and aviganr • covid-19 and T-705 • SARS and T-705	Overall: 5 5 4 2 3 0 0	10 August 2020

Database	URL	Search terms / Search modality	Hits retrieved	Date of search
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and Favipiravir • SARS and favipiravir • covid-19 and avigan • SARS and avigan The following terms were used in addition, where each term was combined with covid-19, or with SARS: T-705, T705, Favipiravirum Abigan Avifavir Areplivir Fabi Flu, Favipira	Overall: 7 6 6 3 4 0	10 September 2020
Citation screening	-	Citation screening of all systematic reviews evaluating favipiravir, identified in NIH LitCovid and NIPH, see Appendix Table 1	10 September 2020	17 systematic reviews (9 additional ongoing trials identified)

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

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