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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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
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
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
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, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the 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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: 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.pdf) 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. Table 1 - Summary of findings (SoF) 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 table 1 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 (Higgins et al., 2019).

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 (DerSimonian 1986). Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used.

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

2. Table 2 - 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

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	Observational studies (comparative or single-arm prospective studies and 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. 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 3 - Ongoing trials:

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

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies.

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 [1].

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.[2, 3]

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 available

Two RCTs have been published evaluating favipiravir in Chinese population.[4, 5] 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.[5] 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).[4] 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 additional phase 2/3 3-arm RCT conducted in Russia was completed evaluating favipiravir with brandname avifavir. As Avifavir instead of avigan was evaluated, the RCT is not embedded in the summary of findings Tables.[6] This trial compared two dosing shedules of avifavir versus standard of case in 60 hospitalized adult patients with moderate COVID-19 (NCT04434248). The comparison was between standard care, avifavir 1600 bid on day 1, followed by 600 mg bid on day 2 to 14 and 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, where only outcome data on viral clearance is reported in sufficient detail.

We did not identify any observational study explicitly reporting to evaluate avigan. Table 4-3 describes four non-randomised observational studies that reported safety outcomes for any brandname of Favipiravir.[7-10] 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 studies.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

The two RCTs were too small to measure effects on all-cause mortality, as no death occurred in either trial arm during the relative short follow-up duration. The certainty of the evidence was very low for both the risk of adverse effects up to 7 days as the SARS-CoV-2 clearance up to 14 days. The current evidence base does not support the use of favipiravir in combination with other medicines for COVID-19.

In the RCT on avifavir, the relative risk of viral clearance in the combined avifavir group at 10 days was 1.16 (95% CI 0.91 to 1.46), meaning that 928 out of 1000 persons would obtain viral clearance in the combined avifavir group and 800 of 1000 would obtain viral clearance in the standard of care group.

4.2 Safety evidence from observational studies

The four observational 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.

4.3 Ongoing studies

There are multiple registered ongoing RCTs, evaluating favipiravir alone or in combination with another pharmacotherapy in Covid-19 patients, in ClinicalTrials.gov and EUdraCT registers. For several of the identified studies, the brandname was not reported. Table 4-4, Table 4-5and Table 4-6 describe ongoing trials for favipiravir of any brandname.

4.4 Scientific conclusion about status of evidence generation

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

Table 4-1. Summary of findings table for published RCTs related to effectiveness and safety of Favipiravir

Patient or population: COVID-19 infection
Setting: Hospital inpatients
Intervention: Favipiravir & standard care with administration of Lopinavir / Ritonavir or Darunavir / Cobicistat and Umifenovir, in combination with interferon α
Comparison: standard care with administration of Lopinavir / Ritonavir or Darunavir / Cobicistat and Umifenovir, in combination with interferon α

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	1000 per 1000	790 per 1000	RR 0.79 (0.54 to 1.15)	19 (1)	very low[a,b]	
Number of patients with respiratory failure and respiratory distress syndrome	400 per 1000	444 per 1000	RR 1.11 (0.39 to 3.19)	19 (1)	very low[a,b]	
All cause mortality			Not estimable	(1)	very low[a,c]	No death occurred during the study period

Source: publication by Lou et al, 2020 [5], Chictr.org.cn trial identifier: ChiCTR200030254. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [11], 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 two levels for very low number of events and very small sample size
c. Downgraded of two levels for very small sample size

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 [4]. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [12], 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[13]	Doi 2020[9]	Yamamura 2020[10]	Calik 2020[8]
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[13]	Doi 2020[9]	Yamamura 2020[10]	Calik 2020[8]
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[13]) • 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	High RoB Very low-quality evidence	High RoB Very low-quality evidence
Overall AEs, n (%)	FV: 4 / 35 (11.43%) L/R: 25 / 45 (55.56%)	-	-	-
Serious AE (SAE), n (%)	-	-	-	-

Author, year	Cai 2020[13]	Doi 2020[9]	Yamamura 2020[10]	Calik 2020[8]
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%)	-
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**
FV = favipiravir; HQ = hydroxychloroquine AZ = azithromycin; L/R = Lopinavir/ritonavir

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

Active substance	Favipiravir	Favipiravir	Favipiravir
Sponsor/Collaborator	Sponsor: Chelsea and Westminster Hospital NHS Foundation Trust, UK Collaborators*: NEAT ID Foundation FUJIFILM Toyama Chemical Co., Ltd. Imperial College London Universitaire Ziekenhuizen Leuven	Sponsor: ASST Fatebenefratelli Sacco	Sponsor: Zhejiang Hisun Pharmaceutical Co. Ltd. Collaborator: Opera CRO, a TIGERMED Group Company
Trial Identifier	EudraCT Number: 2020-001449-38 Clinicaltrials.gov: NCT04373733 Trial acronym: PIONEER	EUdraCT Number: 2020-001115-25 ClinicalTrials.gov Identifier: NCT04336904 Trial acronym: none	ClinicalTrials.gov Identifier: NCT04425460 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	Ongoing (status 13 Aug. 20).	Active, not recruiting	Not yet recruiting
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

Active substance	Favipiravir	Favipiravir	Favipiravir
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary efficacy endpoint: • Time to clinical improvement (post randomisation) by two points on a seven-category ordinal scale# or live discharge from the hospital, whichever comes first. Timepoint: until discharge from inpatient care, 28 day from enrolment or death Secondary endpoints: • Clinical status as assessed with the seven-category ordinal scale at day 7 and day 14 (post- randomisation) • Change in clinical status as assessed with the seven-category ordinal scale at day 7 and day 14 (post- randomisation) relative to baseline • All-cause in-hospital mortality up to day 28 (post randomisation) • Time to clinical response up to day 28 defined as: Time to hospital discharge OR Time to NEWS2 (National Early Warning Score 2) of ≤ 2, maintained for 24 hours(20) • Time to substantial clinical response as defined as: Time to hospital discharge or Time to NEWS2 (National Early Warning Score 2) of ≤ 3, maintained for 24 hours(20) • Time to clinical response up to day 28 (temperature, heartrate, respiratory rate, oxygen saturations) • Number of participants requiring intensive care admission up to day 28 • Duration of intensive care admission • Number of participants requiring mechanical ventilation up to day 28 • Duration of mechanical ventilation • Number of participants requiring non-invasive ventilation, continuous	Primary efficacy endpoint: • Time from randomization to clinical recovery, up to 90 days Secondary outcomes, up to 28 days: • Time from randomization to negativity in RT-PCR nucleic acid test • Incidence of deterioration/aggravation of pneumonia • Time from randomization to resolution of pyrexia • Time from randomization to relief of cough • Time from randomization to relief of dyspnoea • Rate of auxiliary oxygen therapy • ICU admission rate • Mortality	Primary efficacy endpoint: •Time from randomization to clinical recovery, up to 28 days Secondary outcomes, up to 28 days •Negativity in RT-PCR nucleic acid test •Time from randomization to resolution of pyrexia •Time from randomization to relief of cough •Incidence of deterioration/ aggravation of pneumonia •Time from randomization to relief of dyspnoea •Rate of auxiliary oxygen therapy or non-invasive ventilation •ICU admission rate within 28 days of randomization •All-cause mortality within 28 days of randomization

Active substance	Favipiravir	Favipiravir	Favipiravir
	positive airways pressure or high-flow oxygen via (Optiflo ®, Airvo system or equivalent) up to day 28 • Percentage of progression in supplemental oxygen requirement at day 7 • Inflammatory serum makers at day 7 to 10, relative to baseline • Number of participants readmitted to hospital (all-cause) up to day 28 • Proportion of patients with bacterial or fungal infection up to day 28 • Changes in host cytokine profiles at post randomisation time points relative to baseline • Incidence of adverse events not directly caused by COVID-19 infection up to day 28*		
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

For abbreviations see "List of abbreviations" at page x. *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 4-4. Ongoing phase 3 trials of single agents: favipiravir, continued

Active substance	Favipiravir	Favipiravir Single & combination treatment	Favipiravir Single & combination treatment
Sponsor/Collaborator	Sponsor: Ain Shams University	Sponsor: Ministry of Health, Turkey Collaborators: • Hacettepe University, Faculty of Medicine • Prof. Dr. Cemil Tascıoglu Education and Research Hospital Organization • Umraniye Education and Research Hospital • SB Istanbul Education and Research Hospital • Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey • Tepecik Training and Research Hospital • Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine	Beijing Chao Yang Hospital

Active substance	Favipiravir	Favipiravir Single & combination treatment	Favipiravir Single & combination treatment
		• Ankara University • Ankara City Hospital Bilkent • Ankara Training and Research Hospital • Ege University Hospital (Application and Research Center) • Kocaeli Derince Education and Research Hospital • Istanbul University, Istanbul Faculty of Medicine • Kayseri City Hospital	
Trial Identifier	ClinicalTrial.gov: NCT04349241 Trial acronym: FAV-001	ClinicalTrial.gov: NCT04411433 Trial acronym: none	ClinicalTrial.gov: NCT04319900 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	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
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	Single agen 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

Active substance	Favipiravir	Favipiravir Single & combination treatment	Favipiravir Single & combination treatment
		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	
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
Endpoints **Primary Outcomes** **Secondary 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 Secondary outcome, up to 14 days: •Radiological Improvement	Primary efficacy outcome up to 14 days • Time to recovery (discharge) • Decrease in viral load Secondary outcomes, up to 14 days: • Adverse Event (AE), • Serious Adverse Event (SAE) • Discontinuation of treatment • Frequency of occurrence of lymphopenia • Frequency of occurrence of thrombocytopenia • Changes in alanine aminotransferase (ALT) levels; aspartate aminotransferase (AST); C-reactive protein (CRP) D-dimer levels, prothrombin time (PT) values and 5 more from baseline	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 Secondary outcomes up to 10 days: • Duration of fever • Frequencies of progression to severe illness • Time of improvement of pulmonary imaging • and 3 blood marker up to 14 days post intervention period
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

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

Table 4-4. Ongoing phase 3 trials of single agents: favipiravir, continued

Active substance	**Favipiravir**		
Sponsor/Collaborator	Sponsor: R-Pharm		
Trial Identifier	ClinicalTrials.gov Identifier: NCT04501783		
Phase & Intention	Phase 3, treatment Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients With Mild to Moderate COVID-19		
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)		
Status of trial	Active, not recruiting, started May 2020		
Duration/End of Study	August 2020		
Study details			
Number of Patients	168		
Disease severity	Mild to moderate COVID-19		
Setting	In and outpatients		
Location/Centres	Russia, 10 centers in Moscow, Saint Petersburg, Korolev, Voronezh and Zhukovskiy		
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		
Comparator (drug name and dosage)	Standard of Care		
Duration of observation/ Follow-up	Up to day 28		

Active substance	**Favipiravir**		
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary outcomes: • Time to clinical improvement [Time Frame: through Day 28] • Time to viral clearance [Time Frame: through Day 28] Secondary outcomes: • Rate of clinical improvement at separate time points [Time Frame: Day 7] • Rate of viral clearance at separate time points [Time Frame: Days 5 and 7] • Time to body temperature normalization [Time Frame: through Day 28] • Rate of resolution of lung changes on CT [Time Frame: Day 14] • Rate of adverse drug reactions (ADR) and serious ADR [Time Frame: through Day 28] • Rate of severe ADR [Time Frame: through Day 28] • Rate therapy termination due to ADR [Time Frame: through Day 28]		
Results/Publication	None, status 13 Aug. 20		

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

Table 4-5. Ongoing phase 2 trials of single agents: favipiravir

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor/Collaborator	Sponsor: King Abdullah International Medical Research Center Collaborator: Ministry of Health, Saudi Arabia	Sponsor: Ministry of Health, Turkey Collaborators: Hacettepe University, School of Medicine • Prof. Dr. Cemil Tascıoglu City Hospital • Umraniye Training and Research Hospital • Istanbul Training and Research Hospital • Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey • Tepecik Training and Research Hospital • Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine • Ankara University • Ankara City Hospital Bilkent • Ankara Training and Research Hospital • Ege University Hospital (Application and Research Center) • Derince Training and Research Hospital • Istanbul University, Istanbul Faculty of Medicine • Kayseri City Hospital	Sponsor: Appili Therapeutics Inc. Collaborators: • MOUNT SINAI HOSPITAL • Applied Health Research Centre • Sunnybrook Health Sciences Centre • University Health Network, Toronto • University of Toronto
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	Not yet recruiting	Ongoing (status 13 Aug. 20)	Not yet recruiting
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	None	Placebo: 8 tablets orally twice daily on day 1, followed by 4 tablets twice

	9 tablets by mouth twice daily for one day, followed by 4 tablets twice daily (Maximum days of therapy is 7 days)		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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Outcome Measures: • PCR negative [Time Frame: 15 days] • Time from randomization to clinical recovery [Time Frame: 15 days] • Symptoms progression based on clinical evaluation using simple scoring system. [Time Frame: 28 days] 1. Rate of daily requirement of using antipyretics, analgesics, or antibiotics. [Time Frame: 15 days] 2. 28 days mortality. [Time Frame: 28 days] 3. Rate of requirement of hospitalization, ICU admission or Mechanical ventilation. [Time Frame: 28 days] 4. Incidence of Treatment-related Adverse Events [Safety and Tolerability] [Time Frame: 15 days] incidence of GI symptoms secondary to the study drug	• Primary Outcomes: • Time to recovery (discharge) [Time Frame: 7 days] • Decrease in viral load [Time Frame: 7 days] • • Secondary outcomes: • Adverse Event (AE), Serious Adverse Event (SAE) and discontinuation of treatment [Time Frame: 7 days] • Frequency of occurrence of lymphopenia from baseline [Time Frame: 7 days] • Frequency of occurrence of thrombocytopenia from baseline [Time Frame: 7 days] • Changes in alanine aminotransferase (ALT) levels from baseline [Time Frame: 7 days] • Changes in aspartate aminotransferase (AST) levels from baseline [Time Frame: 7 days] • Changes in C-reactive protein (CRP) levels from baseline [Time Frame: 7 days] • Changes in level of D-dimer levels from baseline [Time Frame: 7 days] • Changes in prothrombin time (PT) values from baseline [Time Frame: 7 days] • Changes in partial thromboplastin time (PTT) values from baseline [Time Frame: 7 days] • Changes in blood pressure from baseline [Time Frame: 7 days] • Changes in respiratory rate from baseline [Time Frame: 7 days]	Primary Outcome: • Control of Outbreak [Time Frame: Day 40] Secondary outcomes: • Mortality (Residents) [Time Frame: Day 40, Day 60] • COVID-19 Infection (Residents) [Time Frame: Day 40] • COVID-19 Infection (Staff) [Time Frame: Day 14, Day 40] • Hospitalization (Residents) [Time Frame: Day 40] • Medication Discontinuation (Residents) [Time Frame: Day 40] • Medication Discontinuation (Staff) [Time Frame: Day 40] • COVID-19 in new LTCH Units (a) [Time Frame: Day 40] • COVID-19 in new LTCH Units (b) [Time Frame: Day 40] • COVID-19 in new LTCH Units (c) [Time Frame: Day 40]

		• Changes in pulse oximetry from baseline [Time Frame: 7 days] • Changes in fever from baseline [Time Frame: 7 days]	
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

For abbreviations see “List of abbreviations” at page 4. *as described at clinicaltrials.gov

Table 4-5. Ongoing phase 2 trials of single agents: favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor/Collaborator	Sponsor: Fujifilm Pharmaceuticals U.S.A., Inc.	Sponsor: Royal College of Surgeons in Ireland - Medical University of Bahrain Collaborators: • Ebrahim Khalil Kanoo Community Medical Center • Hereditary blood Disorder Centre – Salmaniya Medical Complex • Mohammed Bin Khalifa Bin Sulman Al Khalifa Cardiac Centre, Awali Jidhafs COVID-19 Centre Sitra FICU	Sponsor: Chromis LLC Collaborator: Chemical Diversity Research Institute
Trial Identifier	ClinicalTrials.gov Identifier: NCT04358549 Other Ids: FAVI-COV-US201 Title: Study of the Use of Favipiravir in Hospitalized Subjects With COVID-19	ClinicalTrials.gov Identifier: NCT04387760 Other Ids: 40 / 07-May-2020 Title: Favipiravir vs Hydroxychloroquine in COVID -19	ClinicalTrials.gov Identifier: NCT04434248 Other Ids: COVID-FPR-01
Phase & Intention	Phase 2, treatment	Phase 2, treatment	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 Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Adaptive, multicenter, open-label, randomized clinical study (Sequential Assignment)
Status of trial	Ongoing (status 13 Aug. 20)	Not yet recruiting	Active, not recruiting, started April 23, 2020
Duration/End of Study	From April 17, 2020 to December 2020	From August 14, 2020 to May 14, 2021	July 2020
Study details			
Number of Patients	50	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 • Scottsdale, Arizona • Miami, Florida • Boston, Massachusetts • Worcester, Massachusetts • Morristown, New Jersey • Houston, Texas	• Irelland, Royal College of Surgeons in 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 Supportive care according to local guidelines	Standard of care (pilot stage) 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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary Outcome: • Time to viral clearance [Time Frame: Day 29] Secondary outcomes: • Status of clinical recovery as measured by the study-specific 6-point ordinal scale on Day 15 [Time Frame: through Day 15] • Clinical effect of favipiravir + SOC compared to SOC	Primary Outcome: • Primary outcome measure will be time to viral clearance [Time Frame: Until discharge or for a maximum of 14 days or readmission] Secondary outcomes: • Requirement of Escalation of Respiratory Support [Time Frame: Until discharge or for a	Primary outcomes: • 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]

	measured by the National Early Warning Score 2 (NEWS2) [Time Frame: through Day 29] • Characterize the pharmacokinetics (PK) of favipiravir in plasma: Cmax) [Time Frame: through Day 14] • Characterized the pharmacokinetics (PK) of favipiravir in plasma: Cmin [Time Frame: through Day 14] • Characterized the pharmacokinetics (PK) of favipiravir in plasma: AUC [Time Frame: through Day 14]	maximum of 14 days or readmission] • Adverse effects(cardiac, renal, hepatic, hypoglycaemia (defined as RBS <3.9 mmol/L)) [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Requirement of ICU Admission [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Mortality rate [Time Frame: Mortality will be collected up to 30 day] • Serum lactate measurement [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Serum Ferritin measurement [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Serum D Dimer measurement [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Ratio of Lymphocyte to Neutrophil, measurement [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Discharge and Length of Hospital Stay [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Readmission Rate [Time Frame: Until 30 days from the start of the trial] • Daily Sequential Organ Failure Assessment (SOFA) score [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Daily National Early Warning Score (NEWS) 2 score [Time Frame: Until	Secondary outcomes: • Rate of viral elimination [Time Frame: Days 3, 5, 7, 9, and 11] • Time to normalization of clinical symptoms [Time Frame: 28 Days] • Duration of oxygen therapy [Time Frame: 28 Days] • Change in the level of lung damage according to CT [Time Frame: Days 15, 22, and 29] • Rate of transfer to the intensive care unit [Time Frame: 28 days] • Rate of the use of non-invasive lung ventilation [Time Frame: 28 days] • Rate of the use of mechanical ventilation [Time Frame: 28 days] • Mortality [Time Frame: 28 days] • Peak plasma concentration (Cmax) [Time Frame: Day 1] • Time to peak plasma concentration (Tmax) [Time Frame: Day 1] • Area under the plasma concentration versus time curve (AUC0-t) [Time Frame: 10 days] Trough plasma concentration (Ctrough) [Time Frame: 10 days]

		discharge or for a maximum of 14 days or readmission] • Clinical improvement [Time Frame: Until discharge or for a maximum of 14 days or readmission] • QT prolongation [Time Frame: Until discharge or for a maximum of 14 days or readmission] • Cardiac arrythmia (fatal and non fatal) [Time Frame: Until discharge or for a maximum of 14 days or readmission]	
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

For abbreviations see “List of abbreviations” at page 4. *as described at clinicaltrials.gov

Table 4-5. Ongoing phase 2 trials of single agents: favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor/Collaborator	Sponsor: Stanford University	Sponsor: Bangladesh Medical Research Council (BMRC)	Sponsor: Bayside Health
Trial Identifier	ClinicalTrials.gov Identifier: NCT04346628	ClinicalTrials.gov Identifier: NCT04402203	ClinicalTrials.gov Identifier: NCT04445467 Title 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, started July 12, 2020	Ongoing, started May 2020 (status 13 Aug. 20)	Not yet recruiting, started July 2020
Duration/End of Study	July 2021	July 2020	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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary outcome: • Time until cessation of oral shedding of SARS-CoV-2 virus [Time Frame: Up to 28 days] Secondary outcomes • Sars-CoV-2 viral load [Time Frame: Up to 28 days] • Count of participants with clinical worsening of COVID-19 disease [Time Frame: Up to 28 days]	Primary outcomes: • 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]	Primary outcome: • Time to virological cure [Time Frame: 14 days] Secondary outcomes: • Safety [Time Frame: 28 days] • Clinical improvement [Time Frame: 28 days] • Clinical symptoms [Time Frame: 28 days] Biomarkers [Time Frame: 28 days]

	• Count of participants with development of SARS-CoV-2 antibodies [Time Frame: Up to 28 days] • Time until cessation of symptoms [Time Frame: Up to 28 days] • Count of participant with absence of development of any symptoms [Time Frame: Up to 28 days] • Cmax of favipiravir [Time Frame: Days 1 and 10 (samples taken 30 minutes prior to and 1 hour following favipiravir administration)] • Cmin of favipiravir [Time Frame: Days 1 and 10 (samples taken 30 minutes prior to and 1 hour following favipiravir administration)]	Secondary outcomes: • Number of participants with clinical recovery [Time Frame: at Day-4, Day-7 and Day-10 of therapy] • Number of participants with adverse effects of drug. [Time Frame: at Day-4, Day-7 and Day-10 of therapy] • Number of participants requiring ICU admission [Time Frame: at Day-4, Day-7 and Day-10 of therapy] • Number of death [Time Frame: at Day-4, Day-7 and Day-10 of therapy]	
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

For abbreviations see “List of abbreviations” at page 4. *as described at clinicaltrials.gov

Table 4-5. Ongoing phase 2 trials of single agents: favipiravir, continued

Active substance	**Favipiravir**	**Favipiravir**	**Favipiravir**
Sponsor/Collaborator	Sponsor: Peking University First Hospital	NHS Greater Glasgow and Clyde / The University of Glasgow, UK	Sponsor: University College London Comprehensive Clinical Trial Unit, UK Collaborator: LifeArc
Trial Identifier	ClinicalTrials.gov Identifier: NCT04310228	EudraCT Number: 2020-001904-41 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
Study design	Study Design: •Allocation: Randomized	Single center two-arm randomised placebo* controlled trial in parallel design. * Although the trial	Multicenter, randomised, double-blind, 2x2 factorial placebo-controlled trial

Active substance	Favipiravir	Favipiravir	Favipiravir
	•Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	was described as placebo controlled, it was also described as open trial, so that the masking method is unclear.	Masking: triple (participant, care provider, investigator)
Status of trial	Recruiting, started March 8, 2020	Ongoing (status 13 Aug. 20)	Ongoing, not yet recruiting*
Duration/End of Study	May 2020	Initial estimation of 1 year, calendar date not reported End of study if one of the following applies: • Six months after the last patient is recruited • Final follow-up visit of the last patient • The stated objectives of the trial are achieved	7-9 months 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 On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 7 days Favipiravir Combined With Tocilizumab group	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
	Favipiravir: On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 7 days. Tocilizumab:The first dose is 4 ~ 8mg/kg and the recommended dose is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg		
Comparator (drug name and dosage)	Tocilizumab group The first dose is 4 ~ 8mg/kg and the recommended dose is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg.	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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary outcome: • Clinical cure rate [Time Frame: 3 months] Secondary outcomes: • Viral nucleic acid test negative conversion rate and days from positive to negative [Time Frame: 14 days after taking medicine] • Duration of fever [Time Frame: 14 days after taking medicine] • Lung imaging improvement time [Time Frame: 14 days after taking medicine]	Primary efficacy endpoint: • reduction in disease severity defined as clinical status as assessed by WHO COVID 10 point ordinal severity scale at day 15. Secondary efficacy endpoints: • Proportion of patients meeting level 7 or above on the WHO COVID 10 point ordinal severity scale or dead by day 29 • WHO COVID 10 point ordinal severity scale level - days 8, 29, 60 • Overall survival - up to and including day 60	Primary outcome: • upper respiratory tract viral load at Day 5 as measured with quantitative polymerase chain reaction (PCR) performed on saliva samples Other outcomes: • Percentage of participants with undetectable upper respiratory tract viral load after 5 days of therapy • Proportion of participants with undetectable stool viral load after 7 days of

Active substance	Favipiravir	Favipiravir	Favipiravir
	• Mortality rate because of Corona Virus Disease 2019 [Time Frame: 3 months] • Rate of non-invasive or invasive mechanical ventilation when respiratory failure occurs [Time Frame: 3 months] Mean in-hospital time [Time Frame: 3 months]	• In patients only - viral clearance on or before day 8 of treatment - day 8 • In patients only - duration of pyrexia in days (define by temperature > 38 degrees C - up to and including day 60	therapy and 14 days post-randomisation • Rate of decrease in upper respiratory tract viral load during 7 days of therapy • Duration of fever following commencement of trial medications • Proportion of participants with hepatotoxicity after 7 days of therapy and 14 days post-randomisation • Proportion of participants with other medication-related toxicity after 7 days of therapy and 14 days post-randomisation • Proportion of participants admitted to hospital with COVID-19 related illness • Proportion of participants admitted to ICU with COVID-19 related illness • Proportion of participants who have died with COVID-19 related illness • Pharmacokinetic and pharmacodynamic analysis of favipiravir • Exploratory: Proportion of participants with deleterious or resistance-conferring mutations in SARS-CoV-2
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

For abbreviations see “List of abbreviations” at page 4. *as described at clinicaltrials.gov

Table 4-5. Ongoing phase 2 trials of single agents: favipiravir, continued

Active substance	Favipiravir	Favipiravir	Favipiravir
Sponsor/Collaborator	Sponsor: Peking University First Hospital	Sponsor: Tanta University	Sponsor: Tanta University
Trial Identifier	ClinicalTrials.gov Identifier: NCT04333589	ClinicalTrials.gov Identifier: NCT04351295	ClinicalTrials.gov Identifier: NCT04345419
Phase & Intention	Not described, treatment Title: Corona Virus Disease 2019 Patients Whose Nucleic Acids	Phase 2/3, treatment	Phase 2/3, treatment

	Changed From Negative to Positive	Title: Efficacy of Faviprevir in COVID-19 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, started April 1, 2020	Not yet recruiting, started April 17, 2020	Recruiting, started June 16, 2020
Duration/End of Study	September 15, 2020	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, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 14 days	Faviprevir	Faviprevir
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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary outcome: • Viral nucleic acid test negative conversion rate [Time Frame: 5 months] Secondary outcome:	Primary outcome: • Number of patients with viral cure [Time Frame: 6 months]	Primary outcome: • Number of patients with decreased viral load [Time Frame: 6 months]

	• Clinical cure rate [Time Frame: 5 months]		
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

For abbreviations see “List of abbreviations” at page 4. *as described at clinicaltrials.gov

Table 4-6. Ongoing trials of combination therapies including favipiravir

Active substance	Favipiravir (Avigan) and + Kaletra (Lopinavir/ritonavir)	Favipiravir and Hydroxychloroquine	Favipiravir and Hydroxychloroquine
Sponsor/Collaborator	Sponsor: University College London Comprehensive Clinical Trial Unit, UK Collaborator: LifeArc	Sponsor: 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	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	Ongoing, not yet recruiting*	Ongoing, recruiting	Not yet recruiting
Duration/End of Study	7-9 months From 17 august 2020 to 1 march 2021	18 months From 21 may 2020 to november 2021	< 1 Months From 20 April 2020 to 5 May 2020 (status last updated at 28 April 2020)
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	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: Avigan (Favipiravir) 200 mg daily 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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary outcome: • upper respiratory tract viral load at Day 5 as measured with quantitative polymerase chain reaction (PCR) performed on saliva samples Other outcomes: • Percentage of participants with undetectable upper respiratory tract viral load after 5 days of therapy • Proportion of participants with undetectable stool viral load after 7 days of therapy and 14 days post-randomisation • Rate of decrease in upper respiratory tract viral load during 7 days of therapy • Duration of fever following commencement of trial medications • Proportion of participants with hepatotoxicity after 7 days of therapy and 14 days post-randomisation • Proportion of participants with other medication-related toxicity after 7 days of therapy and 14 days post-randomisation • Proportion of participants admitted to hospital with COVID-19 related illness • Proportion of participants admitted to	Primary outcome: • 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. Secondary outcome • Viral shedding: PCR test negative conversion days from positive to negative (up to 28 days)	Primary efficacy outcome: •Time to clinical improvement up to 14 days Secondary outcomes, up to 14 days: •Mortality •oxygen saturation by pulse oximetry (SpO2) Improvement •Incidence of new mechanical ventilation use •Duration of hospitalization •Cumulative incidence of serious adverse events

Active substance	Favipiravir (Avigan) and + Kaletra (Lopinavir/ritonavir)	Favipiravir and Hydroxychloroquine	Favipiravir and Hydroxychloroquine
	ICU with COVID-19 related illness • Proportion of participants who have died with COVID-19 related illness • Pharmacokinetic and pharmacodynamic analysis of favipiravir • Exploratory: Proportion of participants with deleterious or resistance-conferring mutations in SARS-CoV-2		
Results/Publication	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

Table 4-6. 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/Collaborator	Sponsor: Hospital General de México Dr. Eduardo Liceaga Collaborators: CCINSHAE. Secretaría de Salud. México Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran Centro de Investigación en. Enfermedades Infecciosas, Mexico	Sponsor: Rajavithi Hospital	Sponsor: Peking University First Hospital	Sponsor: Baqiyatallah Medical Sciences University
Trial Identifier	ClinicalTrials.gov Identifier: NCT04475991 Title Acronym: COMVIVIR	ClinicalTrials.gov Identifier: NCT04303299 Title Acronym:	ClinicalTrials.gov Identifier: NCT04310228	ClinicalTrials.gov Identifier: NCT04376814

Active substance	**Maraviroc+Favipiravir+ Currently used therapy**	**Favipiravir lopinavir /Ritonavir** **Darunavir /ritonavir favipiravir chloroquine**	**Favipiravir Combined With Tocilizumab**	**Favipiravir/Hydroxychloroquine**
		THDMS-COVID-19		
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: Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID-19 : A Randomized Control Trial	Phase not described, treatment Title: Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	Phase not described, treatment 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 two-arm randomised controlled study with parallel group design. PROBE design - prospective randomised open blinded evaluation). Outcome assessors are masked for allocation status.	Multicentter randomized open label controlled trial with parallel group assignment	Randomized open label controlled trial with parallel group assignment
Status of trial	Not yet recruiting, started August 2020	Not yet recruiting, started July 15, 2020	Recruiting, started March 8 2020	Completed, started March 29, 2020
Duration/End of Study	January 2021	March 30, 2021	May 2020	May 25, 2020
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

Active substance	**Maraviroc+Favipiravir+ Currently used therapy**	**Favipiravir lopinavir /Ritonavir** **Darunavir /ritonavir favipiravir chloroquine**	**Favipiravir Combined With Tocilizumab**	**Favipiravir/Hydroxychloroquine**
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 (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga"). 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 (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga"")	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 On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 7 days Favipiravir Combined With Tocilizumab group Favipiravir: On the 1st day, 1600mg each time, twice a day; from the 2nd to the 7th day, 600mg each time, twice a day. Oral administration, the maximum number of days taken is not more than 7 days. Tocilizumab:The first dose is 4 ~ 8mg/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	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.

Active substance	**Maraviroc+Favipiravir+ Currently used therapy**	**Favipiravir lopinavir /Ritonavir** **Darunavir /ritonavir favipiravir chloroquine**	**Favipiravir Combined With Tocilizumab**	**Favipiravir/Hydroxychloroquine**
			single dose does not exceed 800mg	
Comparator (drug name and dosage)	Maraviroc + Currently used therapy Maraviroc tablets. 300 mg bid, given orally for a 10 day period AND Currently used therapy (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga") 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"	Oseltamivir plus Chloroquine in Mild COVID19 Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 800 mg per day In mild COVID19 Darunavir and Ritonavir plus oseltamivir Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus plus Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 400mg per day in Mild COVID19 Lopinavir and Ritonavir plus Oseltamivir in mild COVID19 Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In mild COVID19 Lopinavir and Ritonavir Oseltamivir	Tocilizumab group The first dose is 4 ~ 8mg/kg and the recommended dose is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. Intravenous infusion, The maximum of cumulative number is two, and the maximum single dose does not exceed 800mg.	Hydroxychloroquine 400mg tablets two times per day 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
		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 Qurantine Patient who unwilling to 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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary outcome: • Patients free of mechanical	Primary outcome: • SARS-CoV-2 eradication time	Primary outcome: • Clinical cure rate	Primary outcomes:

Active substance	Maraviroc+Favipiravir+ Currently used therapy	Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine	Favipiravir Combined With Tocilizumab	Favipiravir/Hydroxychloroquine
	ventilation or death [Time Frame: 28 days post start] Secondary outcomes: • Patients free of mechanical ventilation or death [Time Frame: 5 days post start] • Time of clinical improvement [Time Frame: 15 days post start] • Rate of change in phosphorilated CCR5 [Time Frame: Day 10-1] • Rate of change in peripheral blood levels of proinflammatory cytokines and chemokynes [Time Frame: Day 10-1] • Change in the trafficking and activation pattern of peripheral leukocytes [Time Frame: Day 10-1]	[Time Frame: Up to 24 weeks] Secondary outcomes: • Number of patient with Death [Time Frame: Up to 24 weeks] • Number of patient with Recovery adjusted by initial severity in each arm [Time Frame: Up to 24 weeks] • Number of day With ventilator dependent adjusted by initial severity in each arm [Time Frame: Up to 24 weeks] • Number of patient developed Acute Respiratory Distress Syndrome After treatment [Time Frame: Up to 24 weeks] • Number of patient with Acute Respiratory Distress Syndrome Recovery [Time Frame: Up to 24 weeks]	[Time Frame: 3 months] Secondary outcomes: • Viral nucleic acid test negative conversion rate and days from positive to negative [Time Frame: 14 days after taking medicine] • Duration of fever [Time Frame: 14 days after taking medicine] • Lung imaging improvement time [Time Frame: 14 days after taking medicine] • Mortality rate because of Corona Virus Disease 2019 [Time Frame: 3 months] • Rate of non-invasive or invasive mechanical ventilation when respiratory failure occurs [Time Frame: 3 months] • Mean in-hospital time [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 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20	None, status 13 Aug. 20

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