World Health Organization

WHO R&D Blueprint

COVID-19

Informal consultation on the potential inclusion of Favipiravir in a clinical trial

WHO reference number

Geneva, Switzerland, 10th April 2020

R&DBlueprint

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

There has been some suggestions for the inclusion of Favipiravir in the Solidarity trial. Table below shows all trials registered in WHO database these information can be retrieved using the new Web base application. https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/

The highlighted trials has published results for the discussion during the consultation

ChiCTR2000029548	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
ChiCTR2000029600	Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19)
ChiCTR2000030254	Efficacy and Safety of Favipiravir for novel coronavirus–infected pneumonia: A multicenter, randomized, open, positive, parallel-controlled clinical study
ChiCTR2000030113	Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir
ChiCRT2000020894	Favirpiravir combined with Tocilizumab in the treatment of novel coronavirus pneumonia (Covid-19) - A multicentre, randomised controlled trial
ChiCRT2000030987	Clinical trial of favirpiravir tablets combined with chloroquine phosphate in the treatment of novel coronavirus pneumonia (Covid-19)

JPRN-jRCTs031190226	A prospective multi-centre open trial to evaluate the safety and efficacy of Favipiravir in patients infected with covid-19
JPRN-jRCTs041190120	Multicentre, open-label randomised trial of favipiravir in asymptomatic and minimally symptomatic patients infected with SARS-Cov2 to evaluate viral load reduction
NCT04273763	Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19)
NCT04310228	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019

OBJECTIVES OF THE CONSULTATION

Key Questions for Experts

The objective of the call is to discuss whether the new available evidence from the 2 trials in China merit further consideration for evaluation.

This Consultation is part of the standard process for prioritization and represents an initial step towards to an efficacy evaluation of Favipiravir in clinical trials.

There are ongoing efforts to identify additional candidate therapeutics and to expand the body of evidence available on each of the candidates.

Agenda items

1) Welcome and Goals of Ad Hoc Consultation
2) In vitro activity of Favipiravir (Ebola)
3) Existing evidence for clinical benefit from investigations (against influenza)
4) Recent published information from 2 clinical trials (against COVID-19)
5) Recommendations

Working group members

Chair: Marco Cavaleri

Name	Position	Institutional Affiliation
Marco Cavaleri	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Eric Pelfrene	Regulator: Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
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Ross Upshur	Director, Primary Care Research Unit, Sunnybrook and Women's College Health Sciences Centre, Canada Research Chair in Primary Care Research	University of Toronto, Canada
John Beigel	Associate Director for Clinical Research	NIH, USA

Name	Position	Institutional Affiliation
Thomas Fleming	Professor of Biostatistics	University of Washington
John Farley	Director, Office of Infectious Diseases	FDA, USA
Philip Krause	Deputy Director CBER/OVRR	FDA, USA
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OVERVIEW OF THE DELIBERATIONS

Overall considerations

WHO secretariat made a summary of the 2 trials with published results.

Favipiravir versus Lopinavir/Ritonavir: ChiCTR2000029600

The paper was shared with WHO before publication, we just learned days ago the paper has been withdrawn and there is no information about when it will be published. The paper examine the effects of Favipiravir versus Lopinavir /ritonavir in patients with laboratory-confirmed COVID-19 who received oral FPV (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) plus interferon (IFN)-a by aerosol inhalation (5 million U twice daily) were included in the FPV arm of this

study, whereas patients who were treated with LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) plus IFN-a by aerosol inhalation (5 million U twice daily) were included in the control arm.

The trial assessed changes in chest computed tomography, viral clearance, safety, (35 patients FPV arm and the 45 patients in the control arm)

The FPV arm showed faster viral clearance and significant improvement in chest imaging (91.43% versus 62.22% in control). However, the study has some mythological concerns.

Conventional therapy versus favipiravir or arbidol. ChiCTR2000030254

The primary outcome was 7 day's clinical recovery rate. Duration of fever, cough relief time and auxiliary oxygen therapy or non-invasive mechanical ventilation rate were the secondary outcomes. The patients with chest CT imaging and laboratory-confirmed COVID-19 infection, aged 18 years or older were randomly assigned to receive favipiravir or arbidol (120 patients were assigned to favipiravir group and 120 to arbidol group.

Recovery was a bit faster in the favipiravir group, however the study does not show statistical difference, the number of clinical recoveries by day 7 was: 71/116 favipiravir vs 62/120 control 61% vs 52%, so non-significant difference. When the analysis is restricted to mild disease at entry, the number of clinical recoveries by day 7 was 70/98 for favipiravir 62/111 71% vs 56%; so non-significant difference either.

Discussion on the available evidence

1. It was approved in Japan in 2014 for the treatment of novel or re-emerging pandemic influenza virus infections. Use is limited to cases in which other influenza antiviral drugs are not sufficiently effective because favipiravir was only investigated in non-clinical studies in avian influenza A (H5N1 and H7N9),and efficacy against seasonal influenza A or B has not been sufficiently demonstrated. Favipiravir was also trialed for treating Ebola; however, there was no evidence that favipiravir monotherapy was effective.

2. Preclinical data against influenza: FPV was orally administered to mice BID at dosages of 50, 150, or 300 mg/kg/day for 5 days and oseltamivir was used as control. FPV protected mice from lethal infection in a dose-dependent manner. FPV can be effective to protect mice from lethal infection with both wild-type and oseltamivir-resistant influenza B viruses. (Fang et al, 2020)

3. In vitro against Riff Valley Fever, this work shows that favipiravir at concentrations well below the toxicity threshold estimated for cells is able to extinguish RVFV from infected cell cultures.

4. In vitro activity gainst EBOV is IC50 = 60µM and IC90 = 100µM, so normal PK in healthy volunteers is 1000-300µM, so the dosage 600 mg twice a day given to a person will exceed the IC50 in vitro

5. Observational clinical phase III in humans from comparative effectiveness Favipiravir + Oseltamivir versus Oseltamivir with Influenza. (Yeming Wang 2019, Comparative Effectiveness of Combined Favipiravir and Oseltamivir Therapy Versus Oseltamivir Monotherapy in Critically Ill Patients With Influenza Virus Infection). Data from 2 separate prospective studies of influenza were used to compare outcomes between combination and oseltamivir monotherapy. Outcomes included rate of clinical improvement and viral RNA detectability over time. A total of 40 patients who received favipiravir and oseltamivir combination therapy and 128 patients who received oseltamivir monotherapy were included. The conclusion was that favipiravir and oseltamivir combination therapy should be formally evaluated in a randomized controlled trial.

6. Pharmacokinetics: Favipiravir has complex, nonlinear, time and dose dependent PKs are affected by weight. Favipiravir has anti-viral activity as a pro-drug, since favipiravir is intra-cellularly phosphoribosylated to be an active form. It may have potential benefits early in the disease because since it needs 1 day/ ½ to be activated and 2 days/ ½ to have some effect. Even with initial high oral/IV loading dose for adequate blood levels the drug may be useful for pre-exposure or immediate post exposure prophylaxis or at the end of the treatment in convalescent patients to ensure viral clearance.

7. Furthermore, the lower than predicted blood levels (day 4) observed in Ebola virus disease and severe influenza patients raise concerns about bioavailability. (Thi Huyen Tram Nguyen 2016, Favipiravir PKs in Ebola-infected patients of the JIKI trial reveals concentrations lower than targeted). The dosage for Ebola was 6,000 mg loading dose and 2,400 mg for 9 days. (for flu is 1,600 mg loading dose and 600 mg maintenance dose). Higher dosage does not look feasible because of the number of tablets to be taken per day (each tablet is 200mg).

8. There is an ongoing trial for COVID-19 in Japan with 1,800 mg twice as loading dose on Day 1 followed by 800 mg twice a day from Day 2 to 10, which it seems more reasonable, however may only work for mild cases.

9. There are some data that non-Asian people may need higher dose, but is difficult to compare PKs studies in Asia and non-Asian population because the phase I trial was done in Japan for flu and in Guinea for Ebola

10. The human RCT just reported using Arbidol as a comparator ChiCTR2000030254 , the main outcome was clinical recovery by day 7, 71/116 favipiravir vs 62/120 control (61% vs 52%, a non-significant difference). The most encouraging results of the trial were for effects on the rate of auxiliary oxygen treatment or non-invasive mechanical ventilation. Interesting no deaths were reported, even in the control arm in these hospitalized patients. This seems to suggest that these patients may have been hospitalized at very early stage of the disease or with mild symptoms. In conclusion, the Wuhan RCT is not reliable evidence but it may suggest that favipiravir has some activity.

11. The FDA approved 2 phase III trials in 3 Boston Hospitals for COVID-19 and there are another 2 phase III trials in preparation (if funds are available) for treatment of severe cases and pre-symptomatic and mild symptomatic infections in USA. However they have not been registered yet

Conclusions:

1. Favipiravir phase III studies in USA for influenza demonstrated better efficacy than Oseltamivir, however the evidence did not allow the registration.

2. There is a need more preclinical data. Favipiravir might have some benefits in combination with other antiviral to boost antiviral activity or decrease resistance.

3. Need to have vitro data in different cell lines specially HAE cells in a standardized assay, it will allow head to head comparisons of different using same assay conditions. NIH is working with different labs to test different therapeutics in vitro. The BMGF is also looking to generate these data, so they are supporting different groups working Ali Culture and Ephitelix. There has been some delays to set up this screening in human primary cell lines.

4. NIH is working to contract labs to generate data in animal models. BMGF is supporting academic and contract labs o start with hamster model.

5. Analysing 2 RCTs in Wuhan, we need reliable and interpretable data about efficacy and safety of therapeutic interventions in hospitalized COVID-19 there is no statistical difference between the favipiravir and the control arm.

6. Before moving to clinical trials phase IIb/III or to add the favipiravir in to the solidarity trial more evidence need to be generated.

7. As one of the selection criteria is the feasibility of administration, therefore given a high dose that may be needed even for mild cases, it seems difficult to administrate 12 tablets a day and also there are may be issues regarding supply.

8. There is also an issue with the teratogenic potential risk with the use of favipiravir if we consider the risk-benefit in mild cases.

PROPOSED NEXT STEPS

1. Postponement of the discussion until pre-clinical trial evidence in vitro and in vivo will be generated in 1-2 months
2. Collect more information on the PK of favipiravir generated during the Ebola clinical trials
3. A new consultation will be organized when new evidence become available from the planned assays in vitro and vivo coordinated by NIH and also the ones supported by BMGF.
4. WHO secretariat will share with the WG if new data is available from the ongoing clinical trials or new proposals for clinical trials

Note that above prioritization decisions are preliminary and may change as further information is provided to WHO.

Annex

CANDIDATE THERAPEUTIC CHARACTERISTICS Date: 21-04-20

Candidate therapeutic name/denomination: Favipiravir
Manufacturer/developer: Toyama Chemical, from Fujifilm group. Fujifilm licensend API for it to Zhejiang Hisun Pharmaceutical Co. of China
Short description of candidate therapeutic: Antiviral drug developed by Toyama Chemicals in Japan. In experiments conducted in animals Favipiravir has shown activity against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus as well as other flaviviruses, arenaviruses, bunyaviruses and alphaviruses. Favipiravir undergoes an intracellular phosphoribosylation to be an active form, favipiravir-RTP (favipiravir ribofuranosyl-5′-triphosphate), which is recognized as a substrate by RdRp, and inhibits the RNA polymerase activity.
Virus/species/strain: Has been tested against influenza, west nile virus, foot and mouth disease, Ebola, rift valley fever
Proposed indication for use: Indicated for influenza
Target population: *(clarify if for pediatric use and special populations including pregnant women.)* Contraindicated in pregnant and lactating women.
Dose regimen: *(include information on rationale for dose selection and human PK data if available.)* 3x600mg/1d for 14d with loading dose of 1600mg 2x800mg/1d for 14d with loading dose of 1800mg During the Jiki Ebola trial the dosage for Ebola was 6,000 mg loading dose and 2,400 mg for 9 days

Candidate therapeutic name/denomination: Favipiravir
Route of administration: *(Parenteral [IM, ID, SC] as injectable/non-injectable, oral. Please note if special training or equipment or other medications for administration and monitoring are required.)* Oral
Presentation: Tablets 200 mg
Storage & shelf-life: (temperature, stability at given temperature) Temperature stable, no special storage conditions. Shelf life of 36 months
Co-administration with other therapeutics and/or vaccines: Majority of studies are monotherapy, however 3 studies in combination with the following; Alpha-interferon atomization, chloroquine, tocilizumab,
Production: (current number of treatments available, scalability of production process and yield; number of doses per time unit; lead-time) Available in Japan as Avigan and in China as generic
Clinical trials completed ongoing or planned: (complete the form below)
Efficacy: **Pre-clinical efficacy in NHP:** None **Information on surrogate markers:** *(validated or reasonably expected to predict efficacy, e.g. viral load decreases if available.)* **Clinical efficacy data from RCTs:** Pre-clinical studies and Clinical trials completed, ongoing or planned (please complete form below).
Safety data: Generally good safety profile. Due to potential risks for teratogenicity and embryotoxicity that cause congenital disabilities, the Japanese health authorities granted conditional approval for the drug, allowing it only for serious infectious diseases such as avian influenza or Ebola virus.
Registration and WHO prequalification: (status and/or expected timeline)

Pre-clinical Studies and Clinical Trials completed, ongoing or planned.

Candidate therapeutic name: Favipiravir

Date: 21-04-2020

Trial registry number and title	Phase	Recruitment Status	Objectives and target population	Primary outcome measures	Inclusion and exclusion criteria	Design and study arms	Sum of F
ChiCTR2000030254	NA	Recruiting	Treatment infected adults	Clinical recovery at 7 days	Inclusion: 18 years or older, initial symptoms within 12 days, COVID PCR positive.	prospective, randomized, controlled, open-label Favipiravir arm (160) vs arbidol arm (120)	In F coh ord pat CO day rec rate 55.3 the gro 71.4 the favi gro 0.0 ord CO pat CO pat hyp and dial tim red and reli favi gro sig

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Trial registry number and title	**Phase**	**Recruitment Status**	**Objectives and target population**	**Primary outcome measures**	**Inclusion and exclusion criteria**	**Design and study arms**	**Sur of F**

ChiCTR2000030987	2/3	Recruiting	Adults with COVID -19 (18-75 years)	Improvement of respiratory symptoms, viral nucleic acid sheeding	Diagnosis with COVID no more than 14 days ago	Parallel. Favirpiravir (50) + Chloroquine (50) vs Favipiravir vs Control (50)	Ong
ChiCTR2000029600	0	Recruiting	Adults with COVID-19 (16-75 years)	Reducing viral PCR, Negative viral PCR, chest imaging, incidence rate of liver enzymes and kindey damage	Onset within 7 days (temp >38 degrees)	Non randomized Alpha-interferon vs lopinavir + ritonavir +alpha-interferon vs favipiravir +alpha-interferon Target(90)	Ong
NCT04336904	3	Active, not recruiting	Adults with COVID -19 (18-75 years)	Clinical recovery	COVID-19 PCR positive, pneumonia confirmed	Randomised, parallel assignment, double masked Favipiravir vs Placebo (target 100)	Ong
Trial registry number and title	**Phase**	**Recruitment Status**	**Objectives and target population**	**Primary outcome measures**	**Inclusion and exclusion criteria**	**Design and study arms**	**Sur of F**
NCT04319900	2/3	Recruiting	Adults with COVID -19 (18-75 years)	Clinical recovery, days of viral shedding,	Onset within 14 days	Randomised, Parallel, double masked Favipiravir + chloroquine vs favipiravir	Ong

						vs placebo (target 150)	
ChiCTR2000030894	4	Recruiting	Adults with COVID-19 (18-65 years)	Clinical cure rate	Clinical diagnosed with COVID-19	Parallel Favipiravir + Tocilizumab (90) vs Favipiravir (30) vs Tocilizumab (30)	Ong
JPRN-jRCTs031190226	2	Recruiting	Adults with COVID-19	Expected value and 95% CI of ration of C-reactive protein before vs after treatment	PCR positive and temperature > 37.5 degrees	Single arm, no control (50)	Ong
EUCTR2020-1435-27-FR	3	Recruiting	Adults with COVID-19 (18+)	Death, hospitalization Viral carriage,	PCR positive onset <72 hours prior	Randomised, open, parallel, Chloroquine vs favipiravir vs micardis vs imatinibcas vs plaquenil	Ong
ChiCTR2000030113	0	Recruiting	Adults with COVID-19 (16-75 years)	Blood tests, liver function, renal function, blood gas analysis, chest CT	PCR positive, treatment on LPV/RTN for first 10 days	Parallel Lopinavir + Ritonavir (15) vs Favirpiravir (15)	Ong
ChiCTR2000029548	0	Pending	Adults with COVID-19 (18-75 years)	Time to viral negative, time to clinical improvement	PCR positive and onset <96 hours ago	Parallel Baloxavir (10) vs Favipiravir (10) vs LPV/RTN (10)	Ong