World Health Organization

WHO R&D Blueprint

COVID-19

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

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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
Sina Bavari	Independent Consultant	
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Yaseen Arabi	Chairman, Intensive Care Department	King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
John Marshall	Co-Director, Critical Illness and Injury Research Centre, St Michael Hospital, Canada	Co-Director, Critical Illness Research, St Michaels Hospital
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
Regine Lehnert	Regulator	Federal Institute for Drugs and Medical Devices, Germany
Monalisa Chatterji	Senior Program Officer, Discovery & Translational Science	Bill & Melinda Gates Foundation, USA
Michael Kaufmann	Manager- Advisory	PriceWaterhouse Cooper,USA
David Vaughn	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Ken Duncan	Discovery & Translational Sciences team Lead	Bill & Melinda Gates Foundation, USA
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand
Robert Walker	Chief Medical Officer and Director, Division of Clinical Development	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Julia Tree	Microbiological Services	Public Health England
Scott Miller	Deputy Director, medical interventions	Bill & Melinda Gates Foundation, USA

Name	Position	Institutional Affiliation
Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia
Jacqueline Kirchner	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Elizabeth Higgs	Global health science advisor for the Division of Clinical Research (DCR)	NIH. USA
Helen Rees	Professor, Wits Reproductive Health and HIV Institute	University of Witwatersrand, South Africa
Matthew Frieman	Associate Professor, Microbiology and Immunology	University of Maryland School of Medicine

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Kolawole Salami, Emer Cooke, Deusdedit Mubangizi, Matthias Mario Stahl, Raymond Corrin, Philip Coyne

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