Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Potential repurposing of Favipiravir in COVID-19 outbreak based on current evidence

Dear Editor,

As reviewed by Cao et al., the availability of results of previous research studies helped in prioritizing clinical trials for Remdesivir [1]. The molecule was covered in WHO's Director General's opening remarks on February 20, 2020 and is also included in Solidarity Clinical Trial for COVID-19 Treatments [2]. However, due to lack of published results or papers, the panel expressed indecisiveness for prioritization of Favipiravir (Favilavir), which was discovered much earlier than Remdesivir. Since discovery and development of newer drugs take long time, reviewing therapeutic evidence on safety and efficacy of existing drugs and expediting approval of suitable candidates is crucial for quickly providing effective therapeutics to save lives amidst ongoing pandemics like COVID-19, which has resulted in 2,096,573 confirmed cases with around 135,662 deaths globally (as on 16 April 2020).

Favipiravir, a pyrazine carboxamide derivative, is a novel broad-spectrum antiviral drug originally developed many years ago for influenza. It selectively inhibits the influenza viral RNA-dependent RNA polymerase, thereby blocking the process of replication by negatively acting on genetic copying. Due to its activity against RNA viruses, it has been tested against several RNA viruses including H1N1, Ebola, Arena virus, and Bunyavirus. However, it was approved for a few indications in Japan and France and not in other countries.

To assess suitability of Favipiravir for repurposing in COVID-19, we conducted a mini-review of clinical trials using Favipiravir as an investigational drug for various indications in all 18 primary clinical trial registries in the WHO Registry Network and identified 19 such trials.

These trials are summarized below.

Out of 19 Favipiravir trials identified, one dose-escalation trial on Ebola patients (NCT02739477) was terminated due to the end date of the epidemic. Out of remaining 18 trials, fourteen have been completed and four trials on COVID-19 are ongoing in China (see Table 1). Results of only two trials have been published in registries and remaining 12 trials results could not be retrieved from repositories. Study results posted for a multi-centric phase II trial (NCT01068912) [3] demonstrated clinical efficacy of Favipiravir in Influenza, in low-dose as well as high-dose regimens, with no mortality, and no major risk of serious adverse events. Study results for multi-centric phase III trial (NCT02026349) [4] posted on EudraCT revealed that Favipiravir could alleviate symptoms and resolve fever in Influenza without any mortality or serious adverse event. Results of the rest of the 12 completed trials were not available in the registries at the time of writing this article.

It is evident that Favipiravir could result in positive therapeutic outcomes in Influenza. Unavailability of results from > 85% of favipiravir completed clinical trials in registries or in published papers prevented pooling of data and conducting meta-analysis to generate conclusive evidence to support recommendation of Favipiravir use in COVID-19 or know about its safety and efficacy profile.

Many such promising drugs can be overlooked by scientific panels due to lack of conclusive evidence, especially when expedited repurposing and approval of therapeutics effective in pandemic is needed. We might already have available drugs with significant potential to curb the spread of new Coronavirus and prevent significant morbidity and mortality. The authors conclude that reporting of all available

Table 1

Favipiravir past Clinical trials & results availability in the clinical trial registry portals:

S/NO	Clinical Trial	Target Population/ Indication	Current Status	Availability of Result
1	JapicCTI-142657 (Phase I)	Healthy Volunteers	Completed	Not available
2	NCT01419457 (Phase I)	Volunteers with mild to severe hepatic impairment	Completed	Not available
3	NCT01728753 (Phase I)	Mild to severe Influenza	Completed	Not available
4	NCT01068912 (Phase II)	Moderate to severe Influenza	Completed	Available
5	NCT03394209 (Phase II)	Combined Favipiravir and Oseltamivir regimen in Influenza	Completed	Not available
6	NCT02026349 (Phase III)	Influenza	Completed	Available
7	NCT02008344 (Phase III)	Influenza	Completed	Not available
8	UMIN000016101	Ebola in adults	Completed	Not available
9	NCT02329054 (Phase II)	Ebola in all age groups	Completed	Not available
10	NCT02662855 (Phase II)	Severe Ebola Disease in adults	Completed	Not available
11	UMIN000016102	Prevention of Ebola in exposed adults	Completed	Not available
12	UMIN000022398	Severe fever with thrombocytopenia	Completed	Not available
13	UMIN000029020	Severe fever with thrombocytopenia	Completed	Not available
14	JapicCTI-183872 (Phase III)	Severe fever with thrombocytopenia	Completed	Not available
15	ChiCTR2000030113	COVID-19 patients with poor response to Ritonavir	Ongoing	Not available
16	ChiCTR2000029600	COVID-19 Pneumonia	Ongoing	Not available
17	ChiCTR2000029548	Comparing Baloxavir Marboxil, Favipiravir, Lopinavir-Ritonavir in COVID-19 Pneumonia	Ongoing	Not available
18	ChiCTR2000029544	Comparing Baloxavir Marboxil and Favipiravir in COVID-19 positive patients despite antivirals	Ongoing	Not available

<https://doi.org/10.1016/j.tmaid.2020.101710>

Received 12 March 2020; Received in revised form 20 April 2020; Accepted 24 April 2020

Available online 28 April 2020

1477-8939/ © 2020 Elsevier Ltd. All rights reserved.

results and evidence from past clinical trials, even if it indicates failure of interventions evaluated, must be ensured for enabling timely repurposing of effective therapeutics based on scientific evidence from past. Absence of published results from past clinical trials not only hinders future evidence-based research but also may violate data transparency norms set by several countries and undermine ethical standards overall. Through this mini review evaluating prior and ongoing clinical trials on Favipiravir, it is urged that the findings of these trials be made available and disseminated to the scientific community so that it may facilitate timely and crucial understanding of Favipiravir as a potential therapeutic option during COVID-19 pandemic.

Funding source

No funding was received for this study.

Declaration of competing interest

Authors declare no competing interests.

References

- [1] Cao Y, Deng Q, Dai S. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence. *Trav Med Infect Dis* 2020;101647. <https://doi.org/10.1016/j.tmaid.2020.101647>.
- [2] "Solidarity" clinical trial for COVID-19 treatments n.d. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>, Accessed date: 9 April 2020.
- [3] Dose-finding study of favipiravir in the treatment of uncomplicated influenza - full text view - ClinicalTrials.gov n.d. <https://clinicaltrials.gov/ct2/show/NCT01068912>, Accessed date: 9 April 2020.
- [4] Phase 3 efficacy and safety study of favipiravir for treatment of uncomplicated influenza in adults - T705US316 - full text view - ClinicalTrials.gov n.d. <https://clinicaltrials.gov/ct2/show/NCT02026349>, Accessed date: 9 April 2020.

Kapil Khambholja*

Genpro Research Pvt Ltd, Technopark Campus, Thiruvananthapuram,
Kerala, 695581, India

E-mail address: Kapil.khambholja@genproresearch.com.

Deepak Asudani

Department of Medicine, Division of Hospital Medicine, University of
California, San Diego, 92103, USA

E-mail address: dgasudani@health.ucsd.edu.

* Corresponding author.