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.

International Journal of Infectious Diseases 105 (2021) 686–687

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Letter to the Editor

Response to the comments received on article "Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial" by Udwadia et al

We thank Medisetty et al. for their comments on our article "Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial" (Udwadia et al., 2020) and greatly appreciate the opportunity to respond.

The authors queried the inclusion of asymptomatic patients, the use of clinical signs and symptoms to determine severity, oxygen saturation (SpO_2) >95% and cough relief as criteria for clinical cure, the sample size estimation excluding patients from the intention-to-treat (ITT) population, conclusions regarding safety and co-morbidities, medication compliance, and the conclusions on efficacy drawn from secondary outcomes.

Here we state that global trials on favipiravir, including the Stanford trial (NCT04346628), which were conducted during the early pandemic period, included asymptomatic RT-PCR-positive patients along with mild symptomatic patients in order to understand the role of the drug in reducing the duration of viral shedding. Therefore the inclusion of asymptomatic patients in our study was to enhance the understanding of coronavirus disease 2019 (COVID-19). Similarly the use of clinical symptoms and signs to determine the disease severity classification in our study was in line with other global trials, including the remdesivir study (NCT04252664), performed during the period March to April 2020; however, the 'WHO ordinal scale' has since become the standard scale for categorizing COVID-19 severity in clinical trials.

The clinical cure criteria applied in our study included objective parameters of fever, respiratory rate, SpO_2, and cough, and all parameters had to be met for clinical cure to be considered achieved. Our initial study protocol had an SpO_2 requirement of $\geq$98% as one of the criteria for clinical cure. This was later revised based on the updated discharge policy issued by the Ministry of Health and Family Welfare, Government of India, which reported an SpO_2 requirement of >95% (Section 2.1; https://www.mohfw.gov.in/pdf/ReviseddischargePolicyforCOVID19.pdfhttps://www.mohfw.gov.in/pdf/ReviseddischargePolicyforCOVID19.pdf).

The sample size calculation was based on the available data for favipiravir at the time of drafting the protocol in early April 2020 (Cai et al., 2020) and was estimated using the method of Lachin and Foulkes (1986). A sample size of 150 subjects was determined for the study. On subsequent deliberation with regulators, stratified randomization was done based on baseline disease severity as mild (including asymptomatic) (n = 90) and moderate (n = 60) subjects. The standard statistical principle of including patients with at least one post baseline data acquisition was used as a criterion to determine the ITT population (similar to the Remdesivir ACCT-1 study) (Beigel et al., 2020).

Our study was not designed to evaluate efficacy and safety in the patients with co-morbidities. The safety profile of favipiravir was consistent with previous experience of the drug. No adverse events led to discontinuation or a change in the dosing regimen. No new safety signals were noted during the study, hence the conclusion of favipiravir being safe and well tolerated was deemed appropriate. As all of the study patients were hospitalized for the entire duration of the study and the study drug was administered by the site staff in accordance with the protocol and physician recommendations, compliance was not reported in the article. Adherence and missed dose information is more pertinent for studies based in outpatient departments.

It is important to note that the endpoint of clinical cure was allocated as a key secondary endpoint (i.e. the first secondary endpoint), which was significant even if the gate-keeping strategy was used to correct multiplicity for secondary endpoints due to the nature of the study population including mild and moderate cases. Consistency of the efficacy response across end-points led to the conclusions.

We therefore maintain that favipiravir is a promising antiviral agent in patients with mild to moderate symptomatic COVID-19. The median shortening of the time to clinical cure of 3 days versus 5 days demonstrated in our study compares favorably with another oral antiviral agent, oseltamivir, which showed no more than a 16.8 h reduction in a recent Cochrane meta-analysis (Heneghan et al., 2016). This shortened viral shedding could conceivably also have an epidemiological impact by reducing transmission to household contacts. Randomized, double-blind, placebo-controlled trials on favipiravir and its role in household prophylaxis are in the pipeline and will clarify further the role of this drug as an antiviral in COVID-19.

Ethical approval

Not applicable.

Funding source

None.

Conflict of interest

Monika Tandon, Hanmant Barkate, Saiprasad Patil, and Shabbir Rangwala are fulltime employees of Glenmark Pharmaceuticals

http://dx.doi.org/10.1016/j.ijid.2021.02.028

Limited, India. Wen Wu is a full-time employee of Glenmark Pharmaceuticals Ltd, UK. Cynthia Caracta is a full-time employee of Glenmark Pharmaceuticals Inc., USA. Zarir F. Udwadia received an investigator grant from Glenmark Pharmaceuticals Limited, India, as a site principal investigator for this study.

References

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020;383(19):1813–26, doi:http://dx.doi.org/10.1056/NEJMoa2007764.

Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess 2016;20(42):1–242.

https://clinicaltrials.gov/ct2/show/NCT04346628.

https://clinicaltrials.gov/ct2/show/NCT04252664.

Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. Biometrics 1986;42:507–19.

Ministry of Health & Family Welfare Directorate General of Health Services (MoHFW) https://www.mohfw.gov.in/pdf/ReviseddischargePolicyforCOVID19.pdf.

Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020;6(10):1192–8, doi:http://dx.doi.org/10.1016/j.eng.2020.03.007.

Zarir F. Udwadia
Breach Candy Hospital, Mumbai, India

Hanmant Barkate
Saiprasad Patil
Shabbir Rangwala
Glenmark Pharmaceuticals Limited, Mumbai, India

Wen Wu
Glenmark Pharmaceuticals Ltd, Watford, UK

Cynthia F. Caracta
Glenmark Pharmaceuticals, Inc., Mahwah, NJ, USA

Monika Tandon*
Glenmark Pharmaceuticals Limited, Mumbai, India

* Corresponding author.
E-mail address: Monika.Tandon@glenmarkpharma.com (M. Tandon).

Received 5 February 2021