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.

itching than for participants who did not receive paracetamol with this vaccine, as can be seen in the analysis in figure S2 in the appendix,[1] in which the p value for comparison of itching in participants who received paracetamol and participants who did not was p=0·85.

Chauhan and colleagues are correct that an assessment of vaccine efficacy is not usually a part of a phase 2 trial. The large size of the trial and the inclusion of efficacy as an endpoint emphasise the unusual circumstances in which research into COVID-19 vaccines is being done. These are unprecedented times in vaccine research.

We are pleased to read the Correspondence from Archie Lodge, a participant in the trial, and thank him for his time and commitment to participating in this important research. As Lodge rightly points out, maintaining participant masking in any trial is of great importance, as a participant with knowledge of which vaccine they received might alter their behaviour, such as physical-distancing measures, potentially introducing bias into study findings. For this reason, we selected a control vaccine (MenACWY) that also elicited local and systemic reactions in some participants, although reaction rates were lower than for the ChAdOx1 nCoV-19 vaccine. For any individual, it is difficult for them to know whether the reactions that they had were related to the investigational vaccine or the control vaccine. Although some participants might draw conclusions about the vaccine that they received on the basis of figure 1 of our Article,[1] it is important, and standard practice, that safety data are presented openly in this way. We strongly recommend that all trial volunteers continue to protect themselves and their contacts from the pandemic virus by following public health guidance, as participants cannot identify which trial arm they were assigned to until formal unmasking occurs at the end of the trial.

AJP reports grants from the National Institute for Health Research (NIHR) and UK Research and Innovation during the conduct of the study. AJP is Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation but does not participate in discussions on COVID-19 vaccines; and is a member of WHO's Strategic Advisory Group of Experts. The views expressed in this Correspondence do not necessarily represent the views of the Department of Health and Social Care, Joint Committee on Vaccination and Immunisation, NIHR, or WHO. The University of Oxford, Oxford, UK, has entered into a partnership with AstraZeneca on COVID-19 vaccine development.

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Early triple antiviral therapy for COVID-19

In the trial led by Ivan Hung and colleagues,[1] adults admitted to hospital with COVID-19 received two antiviral treatment combinations. In the combination group, 52 (60%) of 86 patients received interferon beta-1b (most patients received one to two doses), lopinavir–ritonavir, and ribavirin, based on the time elapsed from symptom onset to the start of study treatment (median 5 days [IQR 4–7]). However, 34 (40%) patients had interferon beta-1b omitted due to concerns of proinflammatory side-effects in patients who started treatment 7 days or more after symptom onset. In the lopinavir–ritonavir control group, 24 (59%) of 41 patients started treatment less than 7 days from symptom onset, and 17 (41%) started 7 days or more after symptom onset.

Although the results suggest accelerated viral clearance with interferon beta-1b, the clinical efficacy of the triple combination is difficult to assess for several reasons. We are concerned with the absence of a more appropriate control group (either a placebo or no intervention group) and the doubtful efficacy of lopinavir–ritonavir and ribavirin (concerns are summarised in the appendix),[2-4] shown by the non-significant results from the subgroup analysis in the combination group without interferon. Further reasons for concern are the omission of interferon beta-1b in 40% of the intended population, and the clinical efficacy might also be difficult to assess in most patients with mild to moderate COVID-19 symptoms who exhibit quick spontaneous viral clearance and clinical resolution (low baseline national early warning score 2 score of 2 [IQR 1–2], day 1 score of 1 [1–2], and baseline sequential organ failure assessment score of 0 [0–1] in the combination group).[5,6] Additionally, 17 (13%) of 127 patients required supplemental oxygen, six (5%) were admitted to the intensive care unit, 31 (24%) had a normal chest x-ray, and all patients with COVID-19 were admitted to hospital for isolation purposes (according to public health ordinance in Hong Kong). The discharge policy was also linked to providing an RNA negative sample, and finally, the study had insufficient power to detect clinical outcome differences, despite the original intent.

See **Online** for appendix

Thomas Lohnes/Getty Images

Since a modest decrease in RNA might not translate into clinical significance, and data on the infectious virus were unavailable, future controlled studies should focus on confirming the efficacy of interferon-based therapies. Exclusion of ribavirin should be considered because of its potentially harmful side-effects (appendix). Better defined trial criteria to include patients with more severe manifestations are needed, even though studies of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus had not shown substantial safety concerns in later-stage disease.[2,3] Host inflammatory responses are probably important in later-stage COVID-19, thus confounding the assessment of antiviral efficacy in clinical trials. Nonetheless, early intervention trials are important to provide information

on the course of mild to moderate COVID-19 and, possibly, to assess antiviral efficacy overall.[3,4,6]

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Authors' reply

We thank Nelson Lee and colleagues for the important questions. We agree that there are limitations to our study,[1] including the absence of a placebo and no intervention group, which was mentioned in the discussion section of our Article.[1]

As explained in the methods section of the Article,[1] a placebo group was not accepted in Chinese culture and therefore, we had to use lopinavir–ritonavir as a control. We also agree that the efficacy of lopinavir–ritonavir and ribavirin might be weak.[2] Nevertheless, our study was designed in January, 2020, and commenced in early February, 2020, and it was based on results from our previous in-vitro and in-vivo studies,[3,4] in which we found that lopinavir–ritonavir and ribavirin are active against severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus (MERS-CoV). This work was done well before the lopinavir–ritonavir trial[5] was completed and published online in March, 2020. Additionally, most of the trials listed by Lee and colleagues were non-randomised studies on COVID-19 and MERS-CoV. Although 40% of the combination group was not given interferon beta-1b due to late presentation, both the group and subgroup analyses showed high statistical significance, with clinical (national early warning score 2 and sequential organ failure assessment scores) and virological improvement in the combination group. Despite a mild to moderate illness, all patients were symptomatic, and 96 (76%) of 127 patients had pneumonia at baseline. Most patients were admitted to hospital within the first week of symptom onset, and early antiviral treatment probably prevented a substantial proportion of these patients from further deterioration by rapidly reducing viral load and by cytokine suppression. These patients would otherwise have needed a ventilator and intensive care support. The discharge policy was based on two consecutive negative PCR results at least 24 h apart, and all patients were afebrile for 48 h. The 2-week low-dose ribavirin treatment was safe with negligible side-effects, and none of the patients in our study had any harmful drug effects. Overall, our work showed that early interferon-based combination therapy resulted in both clinical and virological improvement in patients with mild to moderate COVID-19. In the future, larger and high-powered studies on interferon-based combination therapy are needed.

We declare no competing interests.

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Clinical trial reporting

Nicholas DeVito and colleagues[1] reported the low compliance with reporting requirements from the Food and Drug Administration Amendments Act of 2007 for results of clinical trials registered on ClinicalTrials.gov, which weakens scientific evidence, violates ethical obligations, and possibly leads to selective publishing.

Since March, 2016, the Chinese Clinical Trial Registry has mandated registrants to report the calculated results for their trials, allowing online public access within 12 months of completion.[2]

To illustrate the compliance of result reporting on this registry, we identified all trials regarding bone fracture

For more on the **Chinese Clinical Trial Registry** see http://www.chictr.org