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.

the small number of participants with chronic lung conditions due to exclusion of those taking corticosteroids, and the self-reported nature of symptoms, which could be inaccurately assessed and biased by multiple factors.

We declare no competing interests.

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1 Yu L-M, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021; **398:** 843–55.

We were encouraged by the results of the PRINCIPLE trial,[1] which in vulnerable individuals showed inhaled budesonide to confer a non-significant –25% (95% CI –45 to 3) relative reduction in the composite coprimary endpoint of hospital admission or death, with the number needed to treat being 50.[1] Notably, the study had 90% power to detect a 50% reduction in the composite endpoint. The investigators appear to have attributed any protective effects of budesonide to its local glucocorticoid activity in the lung.

We were, however, surprised that no mention was made regarding the possibility for appreciable systemic bioavailability of inhaled corticosteroid from the lungs, especially given the high 1600 µg dose of budesonide. For example, in one study of mild asthma patients with a mean forced expiratory volume in 1 s of 86% predicted, treatment for 1 week with 1600 µg budesonide via the same dry powder inhaler device produced –44% (95% CI –47·5 to –40·0) suppression of 24 h serum cortisol relative to placebo.[2] As such, we would welcome comment with regards to the other coprimary endpoint of time to first reported recovery, in particular whether the observed median difference of –2·94 days might be explained by patients feeling better due to a systemic glucocorticoid effect per se rather than a local effect.

Observational health informatics data found that previous use of conventional doses of intranasal corticosteroid were associated with a 22% (95% CI 15–28) reduced risk of hospital admission, a 23% (8–35) reduced need for intensive care, and a 24% (6–39) lower risk of death in hospital for patients with COVID-19.[3] Moreover, these protective effects were replicated when excluding patients with allergic rhinitis and the use of inhaled corticosteroid.

In the meantime, we believe further randomised controlled trials are warranted to investigate whether the use of lower doses of either inhaled budesonide (400 µg) or intranasal budesonide (200 µg), which are devoid of meaningful systemic effects,[2,4] might ameliorate recovery and attenuate disease progression in ambulatory patients with early COVID-19.

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Authors' reply


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We thank Ivan Berezowski and colleagues for highlighting the importance of the PRINCIPLE trial finding a safe, effective, and inexpensive community repurposed medication that shortens COVID-19 illness and reduces the need for hospitalisation and use of oxygen.[1] Most participants (85%) had up to 10 days' illness duration (63% fewer than 7 days in the concurrent population). Inclusion of those almost recovered would reduce rather than increase the chance of showing an effect. In addition, if people without obesity incorrectly reported as people with obesity (32% self-reported a body-mass index >35, but only 27·4% of those were eligible on this criterion alone), this would also probably bias the results towards the null because obesity can be associated with worse outcomes. For patient-reported recovery, asking participants how they feel is appropriate.[2] Indeed, we have reported three treatments not benefiting patient recovery,[3–5] with one tending to worsen[3] patient recovery. Furthermore, several well validated patient-reported outcomes were also used, including the WHO-5 Wellbeing Scale, with differences favouring inhaled budesonide statistically significant at days 7, 14, and 28. Other measures of recovery were modifications of scales used in several large-scale clinical trials shown to be highly responsive to change. All measures showed benefit—while people were recovering, they felt less ill; once recovered they stayed well more often (10% absolute difference, nearly 50% relative difference in sustained recovery over 28 days); and they used fewer health-care resources.