# Asthma drug budesonide shortens recovery time in non-hospitalised patients with COVID-19

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Inhaled budesonide, a common corticosteroid, is the first widely available, inexpensive drug found to shorten recovery times in COVID-19 patients aged over 50 who are treated at home and in other community settings, reports the UK's PRINCIPLE trial in 1,779 participants.

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Early treatment with inhaled budesonide shortens recovery time by a median of three days in patients with COVID-19 who are at higher risk of more severe illness and are treated in the community, finds Oxford University's Platform Randomised Trial of Interventions against COVID-19 in Older People (PRINCIPLE) trial.

PRINCIPLE is the world's largest Phase 3 platform randomised controlled trial to find clear evidence of an effective COVID-19 treatment for use in the community that can significantly shorten recovery time. As one of the UK Government's national priority platform trials, findings from PRINCIPLE have potential to change how COVID-19 is treated in its early stages in non-hospital, community settings in the UK and internationally.

Inhaled budesonide is a safe, relatively inexpensive and readily available corticosteroid commonly used around the world in inhalers to treat asthma and chronic obstructive pulmonary disease. It was added to the PRINCIPLE trial on 28th November 2020.

Recruitment for the inhaled budesonide arm of the trial stopped on 31st March 2021 since, in the view of the Trial Steering Committee, enough patients had been enrolled to establish whether or not the drug had any meaningful benefit on time to recovery. Obtaining further data on hospital admissions or death was unlikely due to the reducing number of cases in the UK.

For the interim report, a total of 961 patients were randomly assigned to receive inhaled budesonide at home and were compared with 1819 patients randomly assigned to the usual standard of NHS care alone. Of these, 751 people in the budesonide group and 1028 in the usual care group were SARS-CoV-2 positive and included in the primary interim analysis.

Based on the interim analysis using the latest data from 25th March 2021, the results showed the estimated median time to self-reported recovery for inhaled budesonide was 3.011 days shorter compared to usual care (95% Bayesian credible interval 1.134 to 5.410 days), with a high probability (0.999) of being superior to the usual standard of care. 32% of those taking inhaled budesonide, compared to 22% in the usual care group, recovered within the first 14 days since being randomised into the trial and subsequently have remained well until 28 days (relative risk 1.46, 95% CI 1.23 - 1.74). Participants in the budesonide group also reported greater wellbeing after two weeks (mean difference in WHO-5 Wellbeing score + 3.37 ,95% CI 0.97 – 5.76, p = 0.006).

Among patients who had completed all 28 days of study follow up by 25th March 2021, 8.5% (59/692) in the budesonide group were hospitalised with COVID-19 compared with 10.3% (100/968) in the usual care group (estimated percentage benefit, 2.1% [95% BCI -0.7% – 4.8%], probability of superiority 0.928). Since fewer than expected people were admitted to hospital in the trial, and with COVID-19 cases and hospitalisations continuing to drop in the UK, it is not clear from this interim analysis whether budesonide reduces hospitalisations.

Patients with COVID-19 symptoms that started within 14 days and who are at higher risk of a poor outcome from the illness could join the trial and those with a positive SARS-CoV-2 result were included in the main analysis. Patients treated with inhaled budesonide were asked to inhale 800 micrograms twice a day for 14 days and were followed-up for 28 days. All patients were aged over 50 with an underlying health condition that put them at more risk of serious COVID-19 illness, or aged over 65.

Joint Chief Investigator, Professor Chris Butler, a South Wales GP and Professor of Primary Care from the University of Oxford's Nuffield Department of Primary Care Health Sciences, said, 'PRINCIPLE, the world's largest platform trial of community-based treatments for COVID-19, has found evidence that a relatively cheap, widely available drug with very few side effects helps people at higher risk of worse outcomes from COVID-19 recover quicker, stay better once they feel recovered, and improves their wellbeing. We therefore anticipate that medical practitioners around the world caring for people with COVID-19 in the community may wish to consider this evidence when making treatment decisions, as it should help people with COVID-19 recover quicker.

'This exciting finding about the beneficial effects of inhaled budesonide would not have been possible without the contribution of those patients who volunteered to participate: your gift of taking part will help doctors and nurses provide better evidence-based care for people with COVID-19 worldwide. It also stands as a monument to the far-sighted funders of PRINCIPLE, the UK-wide clinical research networks who have been absolutely key to the successful implementation of the trial, all the general practices and clinicians who support PRINCIPLE, NHS Digital, HDRUK, the Therapeutics Task Force and the hard work and dedication of our study team and oversight committees in the Primary Care Clinical Trials Unit.'

Joint Chief Investigator, Professor Richard Hobbs, Head of Oxford University's Nuffield Department of Primary Care Health Sciences, said, 'For the first time we have high-quality evidence of an effective treatment that can be rolled out across the community for people who are at most risk of developing more severe illness from COVID-19. Unlike other proven treatments, budesonide is effective as a treatment at home and during the early stages of the illness. This is a significant milestone for this pandemic and a major achievement for community-based research.'

Professor Mona Bafadhel, from Oxford University's Nuffield Department of Medicine, and a Consultant Respiratory Physician, led the earlier STOIC Phase 2 efficacy study of inhaled budesonide for early COVID-19 and led the development of the budesonide study arm for PRINCIPLE. She said, 'The news that the findings of the earlier-phase STOIC trial, which reported at the beginning of the year, have been replicated at scale here in the PRINCIPLE trial is outstanding. We are now sure that we have a treatment that will benefit patients with early COVID-19 worldwide Inhaled budesonide is readily available worldwide and commonly used to treat asthma and chronic obstructive pulmonary disease.'

Professor Fiona Watt, Executive Chair of the Medical Research Council, which co-funded the study, said, 'Researchers involved in the PRINCIPLE trial have overcome considerable logistical hurdles to set up a world-leading rigorous drug trial in people's homes. We are now rewarded with the first inexpensive and widely available drug that can shorten recovery times for COVID-19 patients in the community. People around the world will be helped to recover faster thanks to these exciting new results.'

As soon as all remaining patients in the trial have completed their follow-up and a full analysis has been completed, detailed results on time to recovery and hospitalisations will be published. For this preliminary report, 92.8% of people randomised to the budesonide arm had the opportunity to complete 28 days of follow-up. To read the full pre-print, visit the MedRxiv server (https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1) .

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