Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

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See **Comment** page 609

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of the members of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group is in the appendix

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See **Online** for appendix

Summary

Background Casirivimab and imdevimab are non-competing monoclonal antibodies that bind to two different sites on the receptor binding domain of the SARS-CoV-2 spike glycoprotein, blocking viral entry into host cells. We aimed to evaluate the efficacy and safety of casirivimab and imdevimab administered in combination in patients admitted to hospital with COVID-19.

Methods RECOVERY is a randomised, controlled, open-label platform trial comparing several possible treatments with usual care in patients admitted to hospital with COVID-19. 127 UK hospitals took part in the evaluation of casirivimab and imdevimab. Eligible participants were any patients aged at least 12 years admitted to hospital with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Participants were randomly assigned (1:1) to either usual standard of care alone or usual care plus casirivimab 4 g and imdevimab 4 g administered together in a single intravenous infusion. Investigators and data assessors were masked to analyses of the outcome data during the trial. The primary outcome was 28-day all-cause mortality assessed by intention to treat, first only in patients without detectable antibodies to SARS-CoV-2 infection at randomisation (ie, those who were seronegative) and then in the overall population. Safety was assessed in all participants who received casirivimab and imdevimab. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Findings Between Sept 18, 2020, and May 22, 2021, 9785 patients enrolled in RECOVERY were eligible for casirivimab and imdevimab, of which 4839 were randomly assigned to casirivimab and imdevimab plus usual care and 4946 to usual care alone. 3153 (32%) of 9785 patients were seronegative, 5272 (54%) were seropositive, and 1360 (14%) had unknown baseline antibody status. 812 (8%) patients were known to have received at least one dose of a SARS-CoV-2 vaccine. In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients allocated to casirivimab and imdevimab versus 452 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio [RR] 0·79, 95% CI 0·69–0·91; p=0·0009). In an analysis of all randomly assigned patients (regardless of baseline antibody status), 943 (19%) of 4839 patients allocated to casirivimab and imdevimab versus 1029 (21%) of 4946 patients allocated to usual care died within 28 days (RR 0·94, 95% CI 0·86–1·02; p=0·14). The proportional effect of casirivimab and imdevimab on mortality differed significantly between seropositive and seronegative patients (p value for heterogeneity=0·002). There were no deaths attributed to the treatment, or meaningful between-group differences in the pre-specified safety outcomes of cause-specific mortality, cardiac arrhythmia, thrombosis, or major bleeding events. Serious adverse reactions reported in seven (<1%) participants were believed by the local investigator to be related to treatment with casirivimab and imdevimab.

Interpretation In patients admitted to hospital with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab reduced 28-day mortality in patients who were seronegative (and therefore had not mounted their own humoral immune response) at baseline but not in those who were seropositive at baseline.

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Introduction

Monoclonal antibodies are a set of identical antibodies that have high specificity and affinity for a single epitope. They have been shown to be safe and effective in selected viral diseases when used for prophylaxis (respiratory syncytial virus) or treatment (Ebola virus disease).[1–3] The clinical efficacy of monoclonal antibodies in viral infections is thought to be mediated through direct binding to free virus particles and neutralisation of their ability to infect host cells. Monoclonal antibodies might also bind to viral antigens expressed on the surface of infected cells and stimulate antibody-dependent phagocytosis and cytotoxicity via the crystallisable fragment portion of the antibody.[4]

SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike glycoprotein to angiotensin-converting enzyme 2 on the surface of host cells.[5] The

Research in context

Evidence before this study

We searched MEDLINE, Embase, and medRxiv from Sept 1, 2019, up to Sept 9, 2021, for randomised trials or meta-analyses of trials evaluating the effects of antiviral monoclonal antibody therapy in patients admitted to hospital with COVID-19, using the search terms ("COVID-19", "COVID", "SARS-CoV-2", "2019-nCoV", or "Coronavirus") and ("monoclonal", "REGN-COV2", "casirivimab", "imdevimab", or terms for other specific antiviral monoclonal antibodies identified from clinical trial registries [listed in appendix p 28]). We identified one relevant randomised trial comparing bamlanivimab with placebo in 314 patients admitted to hospital, which was assessed as being at low risk of bias. In the bamlanivimab group, nine of 163 patients died, compared with five of 151 patients in the placebo group (hazard ratio 2·00, 95% CI 0·67–5·99), and no significant difference was seen in the time to sustained recovery (rate ratio 1·06, 95% CI 0·77–1·47).

Added value of this study

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is the largest randomised trial of antiviral monoclonal antibody therapy in patients admitted to hospital with COVID-19. We found that in 3153 COVID-19 patients admitted to hospital without detectable antibodies to SARS-CoV-2 at randomisation (ie, the seronegative group), the monoclonal antibody cocktail of casirivimab 4 g with imdevimab 4 g reduced 28-day mortality, increased the probability of being discharged alive within 28 days, and, among patients who were not receiving invasive mechanical ventilation at randomisation, reduced the probability of progression to the composite outcome of invasive mechanical ventilation or death. The benefits were consistent in all subgroups of seronegative patients. The effect of this treatment differed significantly between patients who were seronegative or seropositive at baseline, with benefit only observed in the seronegative study population.

Implications of all the available evidence

Our findings show that the combination of casirivimab 4 g and imdevimab 4 g given together as a single intravenous infusion improved survival and other clinical outcomes in patients admitted to hospital with COVID-19 who did not have detectable anti-SARS-CoV-2 antibodies (ie, had not yet mounted their own humoral immune response). We observed no clinical benefit in patients who did have detectable anti-SARS-CoV-2 antibodies at baseline.

receptor-binding domain of the spike glycoprotein is, consequently, the main target for neutralising antibodies.[6] Following the emergence of SARS-CoV-2, monoclonal antibodies targeting the spike receptor binding domain were rapidly isolated from humanised mice and from peripheral B cells of recovered patients.[7,8] Anti-SARS-CoV-2 spike protein neutralising monoclonal antibodies have shown in-vivo efficacy in both therapeutic and prophylactic settings in mouse models and non-human primates models, with decreases in viral load and lung pathology.[9–12]

Casirivimab and imdevimab are two non-competing, high-affinity human IgG1 anti-SARS-CoV-2 monoclonal antibodies, which bind specifically to the receptor binding domain of the spike glycoprotein of SARS-CoV-2, blocking viral entry into host cells.[13] A combination of antibodies that bind to non-overlapping epitopes, rather than a single antibody, is intended to minimise the likelihood of loss of antiviral activity due to naturally circulating viral variants or development of escape mutants under drug pressure.[14]

In a clinical study in adult outpatients with SARS-CoV-2 infection and risk factors for severe COVID-19, the combination of casirivimab and imdevimab was well tolerated and, compared with placebo, reduced viral load in the upper airway, shortened the time to symptom resolution, and reduced the composite outcome of COVID-19-related admission to hospital or all-cause mortality.[15,16] The combination of casirivimab and imdevimab has also been shown to prevent SARS-CoV-2 infection in previously uninfected household contacts of infected individuals.[17] Other anti-spike monoclonal antibody products have also shown an antiviral and clinical effect in adult outpatients with SARS-CoV-2 infection.[18,19] In the USA, Emergency Use Authorization has been given by the US Food and Drug Administration for the use of bamlanivimab with etesevimab, casirivimab and imdevimab, and sotrovimab in outpatients with mild to moderate COVID-19. The European Medicines Agency has authorised casirivimab and imdevimab combination for use in patients who are at high risk of progressing to severe COVID-19 but do not require supplemental oxygen. Interim results from a small trial[20] of casirivimab and imdevimab in patients admitted to hospital with COVID-19 requiring low-flow oxygen was consistent with a clinical benefit in seronegative patients.

However, to date, no virus-directed therapy has been shown to reduce mortality in patients admitted to hospital with COVID-19, for whom the only treatments so far shown to reduce mortality have been those that modify the inflammatory response.[21–24] The only published trial of an anti-spike monoclonal antibody (bamlanivimab) in patients admitted to hospital was terminated for futility after 314 patients had been randomly assigned to treatment.[25] Two other substudies of monoclonal antibody products (sotrovimab monotherapy, and BRII-196 with BRII-198 combination therapy) in patients admitted to hospital with COVID-19 were also terminated for futility with sample sizes of 344, and 343, respectively.[26] On first principles, the clinical

response to antibody-based therapies might be greatest in individuals early in disease or those who do not mount an effective immune response. This theory is supported by evidence of clinical benefit in early disease and evidence that baseline anti-SARS-CoV-2 antibody status might be an important predictor of the effect of anti-spike monoclonal antibodies on viral load.[15,16,20,27] A substantial proportion of COVID-19 patients admitted to hospital are seronegative on admission, and although a greater proportion already have detectable anti-SARS-CoV-2 antibodies, the quality of their immunological response might be poor since it has failed to prevent disease progression.[28] As such, anti-spike monoclonal antibodies might have benefit even in later COVID-19 disease. Here we report the results of a large randomised controlled trial of casirivimab and imdevimab combination in patients admitted to hospital with COVID-19.

Methods

Study design and participants

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, platform trial designed to evaluate the effects of potential treatments in patients admitted to hospital with COVID-19. Details of the trial design and results for other possible treatments (dexamethasone, hydroxychloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, convalescent plasma, colchicine, and aspirin) have been published previously.[22,23,28–33] The trial is underway at 177 hospital organisations in the UK supported by the National Institute for Health Research Clinical Research Network (appendix pp 3–27). Of these, 127 UK hospitals took part in the evaluation of casirivimab and imdevimab (Regeneron Pharmaceuticals, Tarrytown, NY, USA). The trial was coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor. The trial is conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Cambridge East Research Ethics Committee (ref: 20/EE/0101). The protocol and statistical analysis plan are in the appendix (pp 69–150) with additional information available on the study website.

Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial. Patients who had received intravenous immunoglobulin treatment during the current admission and children weighing <40 kg or aged <12 years were not eligible for randomisation to casirivimab and imdevimab. Pregnant and breastfeeding women were eligible for inclusion. Written informed consent was obtained from all patients, or a legal representative if they were too unwell or unable to provide consent.

Randomisation and masking

Baseline data were collected using a web-based case report form that included information on demographic characteristics, the level of respiratory support, major comorbidities, suitability of the study treatment for a particular patient, and treatment availability at the study site (appendix pp 34–36). Data on SARS-CoV-2 vaccination status was collected from Dec 22, 2020.

Baseline presence of anti-SARS-CoV-2 antibodies was determined for each participant using serum samples taken at the time of randomisation. Analysis was done at a central laboratory using the Oxford Immunoassay (University of Oxford, Oxford, UK), a validated 384-well plate indirect ELISA for anti-spike IgG (appendix p 28).[34] Participants were categorised as seropositive or seronegative using a predefined assay threshold with a 99% or higher sensitivity and specificity in detecting individuals with SARS-CoV-2 infection at least 20 days previously.[34] Post-hoc sensitivity analyses were done using commercially available immunoassays for total anti-spike and anti-nucleocapsid antibodies (Roche Diagnostics, Basel, Switzerland) with the seropositive thresholds defined as greater than 0·8 and greater than 0·1, respectively (appendix p 28).

For more on the **RECOVERY trial** see https://www.recoverytrial.net

Eligible and consenting patients were assigned (1:1:1) to either usual standard of care, usual standard of care plus casirivimab and imdevimab (antibody combination), or usual standard of care plus convalescent plasma (until Jan 15, 2021), using web-based simple (unstratified) randomisation with allocation concealed until after randomisation (appendix pp 32–34). The trial was not designed to directly compare convalescent plasma versus casirivimab and imdevimab, and the comparison of convalescent plasma versus usual care has been previously reported.[28] For some patients, the antibody combination was unavailable at the hospital at the time of enrolment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. These patients were excluded from the randomised comparison between casirivimab and imdevimab versus usual care.

As a platform trial, and in a factorial design, patients could be simultaneously randomly assigned to other treatment groups: azithromycin, colchicine, aspirin, or baricitinib versus usual care. Further details of when these factorial assignments were open is in the appendix (pp 32–34). Until Jan 24, 2021, the trial also allowed a subsequent random assignment for patients with progressive COVID-19 (evidence of hypoxia and a hyperinflammatory state) to tocilizumab versus usual care. Participants and local study staff were not masked to the allocated treatment. The trial steering committee, investigators, and all other individuals involved in the trial were masked to analyses of outcome data during the trial.

Procedures

Patients allocated to the antibody combination were to receive a single dose of casirivimab 4 g and imdevimab 4 g administered together in 250 ml 0·9% saline infused intravenously over 60 min (plus or minus 15 min) as soon as possible after randomisation. The dose of 4 g per antibody was chosen to maximise the probability of a therapeutic effect while ensuring patient safety, based on preliminary data from inpatient (NCT04426695) and outpatient (NCT04425629) studies of the safety, tolerability, and efficacy of casirivimab and imdevimab (unpublished data, Regeneron Pharmaceuticals).

Early safety outcomes were recorded by site staff using an online form 72 h after randomisation (appendix pp 37–41). An online follow-up form was completed by site staff when patients were discharged, had died, or at 28 days after randomisation, whichever occurred first (appendix pp 42–48). Information was recorded on adherence to allocated trial treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, and vital status (including cause of death). In addition, routinely collected health-care and registry data were obtained, including information on vital status at day 28 (with date and cause of death), discharge from hospital, and receipt of respiratory support or renal replacement therapy.

Outcomes

Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital, and, in patients not on invasive mechanical ventilation at randomisation, the composite outcome of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death. Pre-specified subsidiary clinical outcomes were use of invasive or non-invasive ventilation among patients not on any ventilation at randomisation, time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days), and use of renal replacement therapy (dialysis or haemofiltration). Information on suspected serious adverse reactions was collected in an expedited way to comply with regulatory requirements. Details of the methods used to ascertain and derive outcomes are in the appendix (pp 151–71).

Pre-specified safety outcomes were cause-specific mortality, major cardiac arrhythmia, and thrombotic and major bleeding events (only collected since Nov 6, 2021). Information on early safety outcomes at 72 h after randomisation (worsening respiratory status, severe allergic reactions, fever, sudden hypotension, clinical haemolysis, and thrombotic events) ceased on Feb 19, 2021, on the advice of the study's data monitoring committee and in accordance with the protocol.

Statistical analysis

For all outcomes, we did intention-to-treat analyses comparing patients randomly assigned to casirivimab and imdevimab with patients who were randomly assigned to usual care but for whom the antibody combination was both available and suitable as a treatment. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used to both test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the average mortality rate ratio (RR). We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used the same method to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital censored on day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the pre-specified composite secondary outcome of progression to invasive mechanical ventilation or death within 28 days (in those not receiving invasive mechanical ventilation at randomisation), and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so the risk ratio was estimated instead. Estimates of rate and risk ratios are shown with 95% CI.

In the light of new evidence that became available during the trial, it was hypothesised that any beneficial effect of casirivimab and imdevimab would be larger among seronegative participants (and might be negligible in seropositive participants).[20,35] Consequently, before any unmasking of results, the trial steering committee specified that hypothesis-testing of the effect of allocation to casirivimab and imdevimab on the primary outcome of 28-day mortality (and secondary outcomes) would first be done only in seronegative participants (ie, those without detectable antibodies to SARS-CoV-2 infection; appendix pp 144–46). Hypothesis testing of the primary outcome in all randomly assigned patients was then only to be done if a reduction in mortality in seronegative patients was noted with a two-sided p value of less than 0·05. A prespecified comparison of the effects of allocation to casirivimab and imdevimab on 28-day mortality in seronegative versus seropositive participants was done by performing a test for heterogeneity. Tests for heterogeneity or trend according to other baseline characteristics (age, sex, ethnicity, level of respiratory support, days since symptom onset, and use of corticosteroids; appendix pp 135–36) were also pre-specified.

The full database is held by the study team, which collected the data from study sites and performed the analyses at the Nuffield Department of Population Health, University of Oxford (Oxford, UK).

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the COVID-19 pandemic. On April 27, 2021,

the trial steering committee, whose members were unaware of the results of the trial comparisons, determined that, with more than 9700 patients recruited to the casirivimab and imdevimab comparison and average daily recruitment of four patients, further recruitment was unlikely to increase the reliability of the results materially and so should discontinue (appendix p 34). The statistical analysis plan was finalised and published on May 21, 2021 (without any knowledge of the study results; appendix pp 114–50) and recruitment to the casirivimab and imdevimab comparison was closed on May 22, 2021. The trial steering committee and all other individuals involved in the trial were masked to outcome data until after the close of recruitment (appendix p 49). Analyses were performed using SAS version 9.4 and R version 4.0.3. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Regeneron Pharmaceuticals supported the study through supply of casirivimab and imdevimab and DMW provided comments on the manuscript as a member of the writing committee.

Results

Between Sept 18, 2020, and May 22, 2021, 11 464 (47%) of 24 343 patients enrolled into the RECOVERY trial at one of the 127 participating sites were eligible to be randomly assigned to casirivimab and imdevimab (ie, the treatment was available in the hospital at the time and the attending clinician was of the opinion that the patient had no known indication for or contraindication to it; figure 1). Of these patients, 4839 were randomly assigned to casirivimab and imdevimab combination and 4946 were randomly assigned to usual care. The mean age of study participants in this comparison was 61·9 years (SD 14·5) and the median time since symptom onset was 9 days (IQR 6–12; appendix p 52).

The characteristics of patients considered unsuitable for this comparison are in the appendix (p 51). At randomisation, 5272 (54%) were seropositive at baseline, 3153 (32%) were seronegative, and serostatus was unknown for 1360 (14%). Other baseline characteristics including receipt of corticosteroids and SARS-CoV-2 PCR test results are in table 1 and the appendix (p 52). 812 (8%) were known to have received at least one dose of a SARS-CoV-2 vaccine.

The follow-up form was completed for 4790 (99%) of 4839 patients in the casirivimab and imdevimab group and 4916 (99%) of 4946 patients in the usual care group. Among patients with a completed follow-up form, 90% assigned to casirivimab and imdevimab received casirivimab and imdevimab; no patients assigned to usual care received casirivimab and imdevimab (figure 1; appendix p 53). Use of other treatments for COVID-19 was similar among

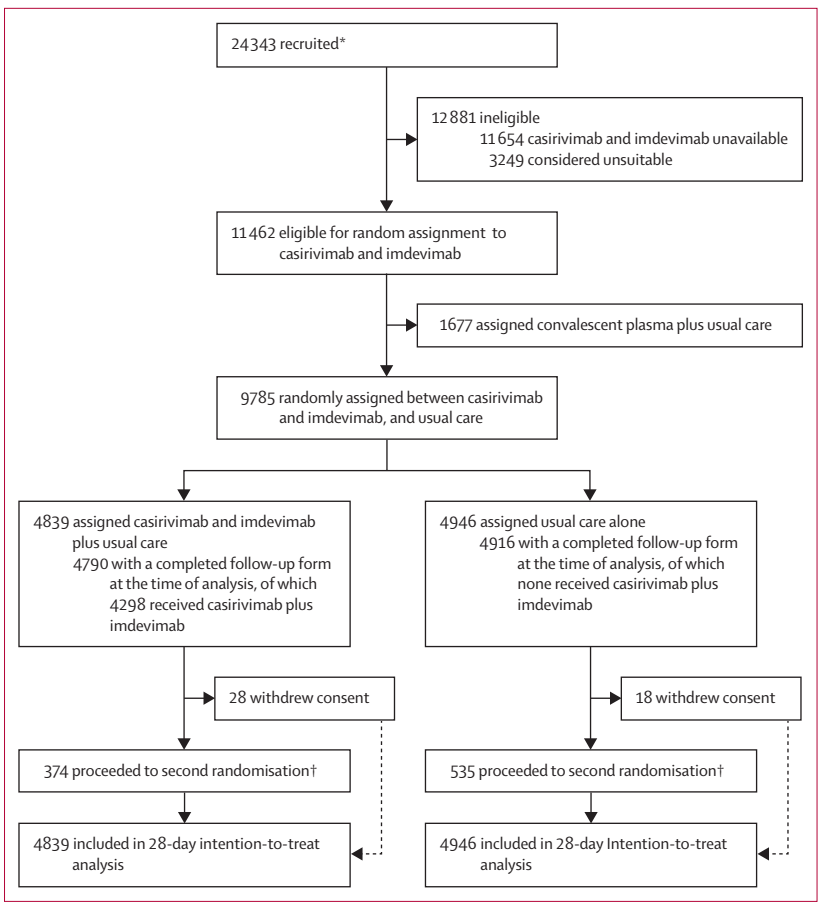

Figure 1: **Trial profile**
Casirivimab and imdevimab unavailable and casirivimab and imdevimab unsuitable groups are not mutually exclusive. *Number recruited overall during the period that adult participants could be recruited into the casirivimab and imdevimab comparison. †Includes patients allocated to tocilizumab. Until Jan 24, 2021, tocilizumab was allocated via the second randomisation to 185 (4%) of 4839 patients allocated casirivimab and imdevimab and to 271 (5%) of 4946 patients allocated to usual care.

patients allocated casirivimab and imdevimab and among those allocated usual care, with about 25% receiving remdesivir and about 15% receiving tocilizumab or sarilumab (appendix p 53).

Primary and secondary outcome data are known for more than 99% of randomly assigned patients. In patients who were known to be seronegative at baseline, allocation to casirivimab and imdevimab was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone: 396 (24%) of 1633 patients in the casirivimab and imdevimab group died versus 452 (30%) of 1520 patients in the usual care group (RR 0·79, 95% CI 0·69–0·91; p=0·0009; table 2, figure 2, figure 3). The proportional effect of casirivimab and imdevimab on mortality differed significantly between seropositive and seronegative patients (test for heterogeneity p=0·002; figure 3). Among all randomly assigned patients (including those with negative, positive, or unknown baseline antibody status), there was no significant difference in the primary

	Seronegative patients		All patients	
	Casirivimab and imdevimab (n=1633)	Usual care (n=1520)	Casirivimab and imdevimab (n=4839)	Usual care (n=4946)
Age, years	63·2 (15·5)	64·0 (15·2)	61·9 (14·6)	61·9 (14·4)
<70*	1054 (65%)	943 (62%)	3389 (70%)	3454 (70%)
70–79	348 (21%)	344 (23%)	936 (19%)	962 (19%)
≥80	231 (14%)	233 (15%)	514 (11%)	530 (11%)
Sex				
Men	995 (61%)	879 (58%)	3033 (63%)	3095 (63%)
Women†	638 (39%)	641 (42%)	1806 (37%)	1851 (37%)
Ethnicity				
White	1325 (81%)	1254 (83%)	3779 (78%)	3822 (77%)
Black, Asian, and minority ethnic	151 (9%)	136 (9%)	596 (12%)	697 (14%)
Unknown	157 (10%)	130 (9%)	464 (10%)	427 (9%)
Number of days since symptom onset	7 (4–10)	7 (5–9)	9 (6–12)	9 (6–12)
Number of days since admission to hospital	1 (1–2)	1 (1–3)	2 (1–3)	2 (1–3)
Respiratory support received				
No oxygen received	182 (11%)	148 (10%)	332 (7%)	309 (6%)
Simple oxygen	1085 (66%)	995 (65%)	2980 (62%)	3016 (61%)
Non-invasive ventilation	332 (20%)	341 (22%)	1244 (26%)	1317 (27%)
Invasive mechanical ventilation	34 (2%)	36 (2%)	283 (6%)	304 (6%)
Previous diseases				
Diabetes	403 (25%)	407 (27%)	1240 (26%)	1337 (27%)
Heart disease	407 (25%)	398 (26%)	1038 (21%)	1061 (21%)
Chronic lung disease	455 (28%)	458 (30%)	1085 (22%)	1159 (23%)
Tuberculosis	7 (<1%)	5 (<1%)	18 (<1%)	16 (<1%)
HIV	7 (<1%)	4 (<1%)	24 (<1%)	22 (<1%)
Severe liver disease‡	28 (2%)	17 (1%)	69 (1%)	70 (1%)
Severe kidney impairment§	114 (7%)	114 (8%)	266 (5%)	242 (5%)
Any of the above previous diseases	935 (57%)	913 (60%)	2557 (53%)	2662 (54%)
SARS-CoV-2 PCR test result				
Positive	1587 (97%)	1476 (97%)	4702 (97%)	4813 (97%)
Negative	19 (1%)	16 (1%)	42 (1%)	56 (1%)
Unknown	27 (2%)	28 (2%)	95 (2%)	77 (2%)
SARS-CoV-2 antibody test result				
Positive	0	0	2636 (54%)	2636 (53%)
Negative	1633 (100%)	1520 (100%)	1633 (34%)	1520 (31%)
Missing	0	0	570 (12%)	790 (16%)
Received a COVID-19 vaccine	128 (8%)	117 (8%)	394 (8%)	418 (8%)
Corticosteroids received				
Yes	1481 (91%)	1399 (92%)	4530 (94%)	4639 (94%)
No	152 (9%)	118 (8%)	308 (6%)	299 (6%)
Not recorded	0	3 (<1%)	1 (<1%)	8 (<1%)
Other randomly assigned treatments				
Azithromycin	38 (2%)	43 (3%)	124 (3%)	124 (3%)
Colchicine	364 (22%)	350 (23%)	1085 (22%)	1139 (23%)
Aspirin	405 (25%)	372 (24%)	1339 (28%)	1389 (28%)
Baricitinib	139 (9%)	138 (9%)	440 (9%)	422 (9%)

Data are mean (SD), n (%), or median (IQR). *Includes 11 children (aged <18 years). †Includes 26 pregnant women. ‡Defined as requiring ongoing specialist care. §Defined as estimated glomerular filtration rate lower than 30 mL/min per 1·73 m^2.

Table 1: **Baseline characteristics of the study population**

outcome of 28-day mortality between the casirivimab and imdevimab versus the usual care groups: 943 (19%) of 4839 patients in the casirivimab and imdevimab group died versus 1029 (21%) of 4946 patients in the usual care group (RR 0·94, 95% CI 0·86–1·02; p=0·14; figure 2, figure 3, appendix p 54). Similar results were noted in post-hoc sensitivity analyses using a commercial immunoassay to define either anti-S or anti-N serostatus (appendix pp 62–63).

In seronegative patients, the proportional effects of casirivimab and imdevimab on mortality were consistent across all other pre-specified subgroups (figure 4), including by the level of respiratory support received at randomisation (test for trend p=0·55; figure 4) and, in a post-hoc exploratory analysis, by use of remdesivir at baseline (test for heterogeneity p=0·36; appendix p 64), and by baseline C-reactive protein concentration divided into thirds (test for trend p=0·22). Likewise, among all randomly assigned patients combined (ie, irrespective of serostatus), there was similar consistency across subgroups (appendix p 65). Results were also similar when restricted to participants with a positive SARS-CoV-2 PCR test (appendix p 55). In a sensitivity analysis using a Cox model adjusted for all pre-specified subgroups, allocation to casirivimab and imdevimab was associated with a mortality RR of 0·85 (95% CI 0·74–0·97) in seronegative patients (appendix p 55). In all participants, there was no evidence that the effect of casirivimab and imdevimab on mortality varied depending on concurrent randomised allocation to azithromycin, colchicine, or aspirin (all interaction p values >0·11).

In seronegative patients, discharge alive within 28 days was more common for those assigned to casirivimab and imdevimab than those assigned to usual care (table 2, figure 3, appendix p 66). However, there was no meaningful between-group difference in the overall study population for this outcome (median 10 days [IQR 6 to >28] *vs* 10 days [5 to >28]; figure 3, appendix p 54).

In seronegative patients not on invasive mechanical ventilation at baseline, casirivimab and imdevimab was associated with a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (table 2, figure 3). However, there was no between-group difference in the overall study population (figure 3, appendix p 54).

The proportional effects of casirivimab and imdevimab on the secondary outcomes of discharge alive from hospital and invasive mechanical ventilation or death differed significantly between seropositive and seronegative patients (p value for heterogeneity for both <0·001; figure 3). In all participants (irrespective of baseline serostatus), there was no evidence of differences in secondary outcomes in prespecified subgroups of patients (appendix pp 67–68).

In patients who were not on ventilation at baseline, casirivimab and imdevimab was associated with less frequent progression to use of ventilation than usual care in those who were seronegative (table 2) but not in the overall study population (appendix p 54). There were no meaningful differences in progression to renal replacement therapy, non-COVID mortality, cardiac arrhythmia, thrombosis, or major bleeding either in the seronegative or overall study populations (table 2, appendix pp 56–58).

	Casirivimab and imdevimab (n=1633)	Usual care (n=1520)	RR (95% CI)
Primary outcome			
Mortality at 28 days	396 (24%)	452 (30%)	0·79 (0·69–0·91)
Secondary outcomes			
Median duration of hospitalisation, days	13 (7 to >28)	17 (7 to >28)	··
Discharged from hospital within 28 days	1049 (64%)	878 (58%)	1·19 (1·09–1·31)
Invasive mechanical ventilation or death*	488/1599 (31%)	544/1484 (37%)	0·83 (0·75–0·92)
Invasive mechanical ventilation	190/1599 (12%)	202/1484 (14%)	0·87 (0·73–1·05)
Death	383/1599 (24%)	435/1484 (29%)	0·82 (0·73–0·92)
Subsidiary outcomes			
Use of ventilation†	360/1267 (28%)	373/1143 (33%)	0·87 (0·77–0·98)
Non-invasive ventilation	348/1267 (27%)	362/1143 (32%)	0·87 (0·77–0·98)
Invasive mechanical ventilation	90/1267 (7%)	120/1143 (10%)	0·68 (0·52–0·88)
Successful cessation of invasive mechanical ventilation‡	10/34 (29%)	10/36 (28%)	1·19 (0·49–2·88)
Renal replacement therapy§	67/1614 (4%)	65/1498 (4%)	0·96 (0·69–1·34)

Data are n (%), median (IQR), or n/N (%). RR=rate ratios for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratios for other outcomes. *Excluding patients receiving invasive mechanical ventilation at randomisation. †Excluding patients receiving invasive or non-invasive ventilation at randomisation. ‡Excluding patients not receiving invasive mechanical ventilation at randomisation. §Excluding patients receiving renal replacement therapy at randomisation.

Table 2: **Effect of allocation to casirivimab and imdevimab on key study outcomes in seronegative participants**

Information on potential infusion reactions occurring within the first 72 h after randomisation was collected for 1792 patients in the casirivimab and imdevimab group and 1715 patients in the usual care group (before collection of these data stopped on Feb 19, 2021). In the overall study population, the reported frequency of fever (in 79 [4%] of 1792 *vs* 52 [3%] of 1715), sudden hypotension (66 [4%] *vs* 39 [2%]), and thrombotic events (31 [2%] *vs* 24 [1%]) was numerically higher in the casirivimab and imdevimab group versus the usual care group, and the frequency of sudden worsening in respiratory status (369 [21%] *vs* 372 [22%]) and clinical haemolysis (26 [1%] *vs* 31 [2%]) was numerically lower (appendix p 59). There were seven reports (<1% of particpants) of a serious adverse reaction believed to be related to treatment with the combination of casirivimab and imdevimab (three allergic reactions, two seizures, one acute desaturation, and one transient loss of consciousness; appendix p 60), and no deaths attributed to the treatment.

Discussion

In this large, randomised trial, casirivimab and imdevimab antibody combination in patients who were anti-SARS-CoV-2 antibody negative (ie, had not yet

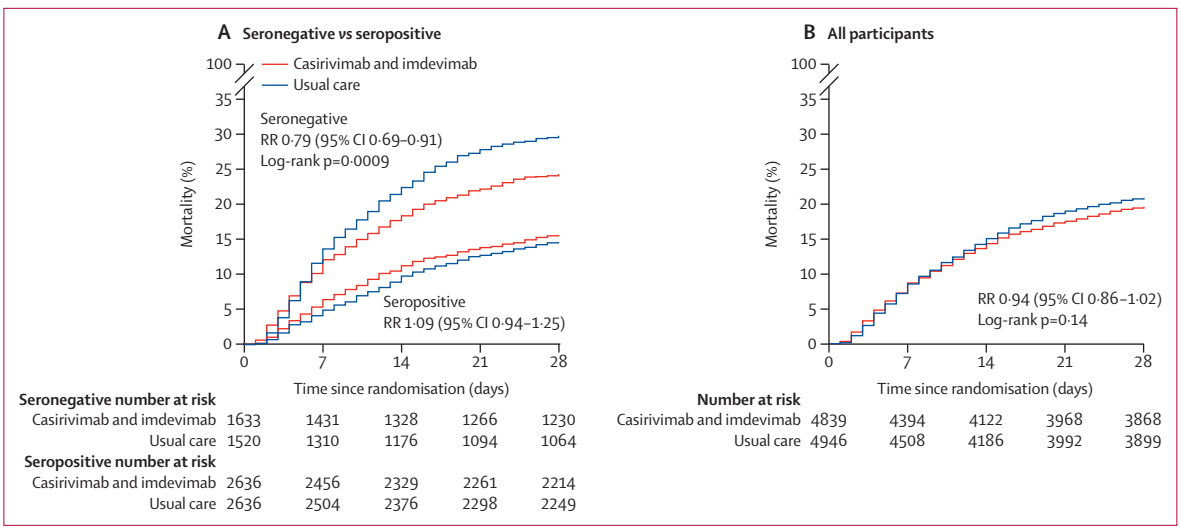

Figure 2: **Effect of allocation to casirivimab and imdevimab on 28-day mortality in (A) seronegative patients versus seropositive patients and (B) all participants overall**
RR=rate ratio.

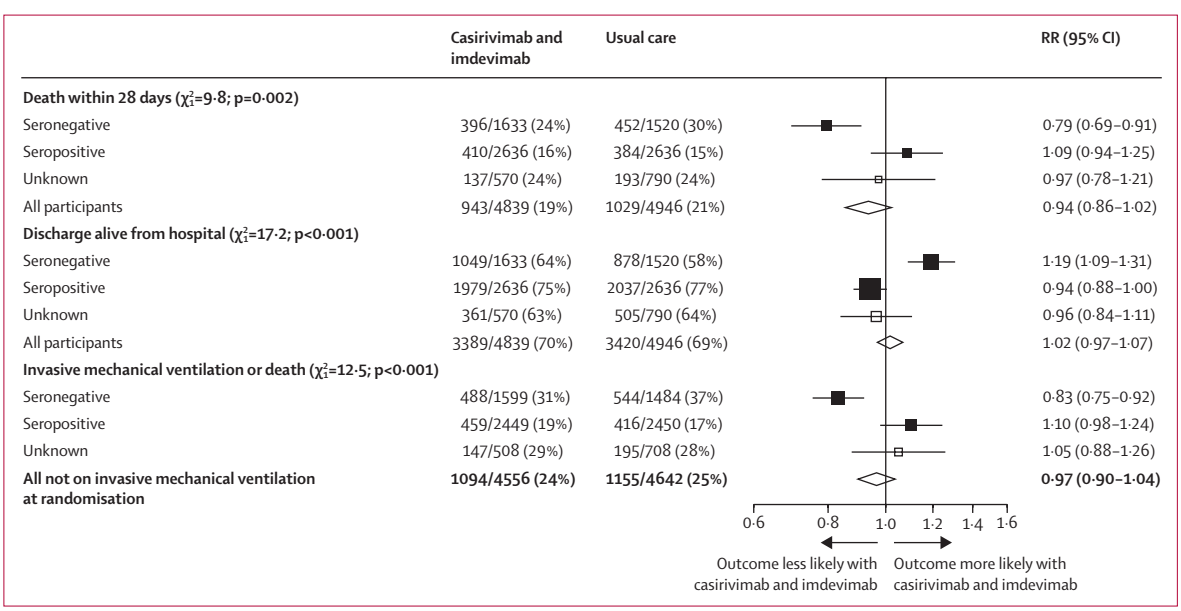

Figure 3: **Primary and secondary outcomes, overall and by baseline antibody status**
Subgroup-specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. Open squares represent participants with unknown status, solid squares represent participants with known status. The tests for heterogeneity (ie, χ^2_1) compare the log RRs in the seronegative versus seropositive subgroups (ie, excluding those with unknown antibody status). Excluded participantsare included in the overall summary diamonds. RR=risk ratio for the composite outcome of invasive mechanical ventilation or death, and rate ratio for the other outcomes.

mounted their own humoral immune response) significantly reduced 28-day mortality by about one-fifth compared with usual care, an absolute benefit of six fewer deaths per 100 patients allocated the treatment. In addition, casirivimab and imdevimab was associated with an increased rate of discharge alive from hospital within the first 28 days and a reduced rate of progression to invasive mechanical ventilation or death in these patients. By contrast, no such benefits were seen for patients who were anti-SARS-CoV-2 antibody positive at randomisation. Consequently, when all patients were considered together (including those with unknown antibody status), casirivimab and imdevimab was associated with non-significant differences in clinical outcomes. Randomised clinical trials of three neutralising monoclonal antibody preparations (LY-CoV555, sotrovimab, and BRII-196 with BRII-198) in patients admitted to hospital for

	Casirivimab and imdevimab	Usual care	RR (95% CI)
Age, years (χ^2_1=0·8; p=0·39)			
<70	147/1054 (14%)	157/943 (17%)	0·82 (0·66–1·03)
70 to 79	123/348 (35%)	161/344 (47%)	0·71 (0·56–0·90)
≥80	126/231 (55%)	134/233 (58%)	0·97 (0·76–1·25)
Sex (χ^2_1=0·9; p=0·33)			
Men	261/995 (26%)	270/879 (31%)	0·83 (0·70–0·99)
Women	135/638 (21%)	182/641 (28%)	0·73 (0·58–0·91)
Ethnicity (χ^2_1=0·1; p=0·77)			
White	336/1325 (25%)	396/1254 (32%)	0·78 (0·67–0·90)
Black, Asian, or minority ethnic	27/151 (18%)	33/136 (24%)	0·72 (0·43–1·20)
Days since symptom onset (χ^2_1=0·4; p=0·54)			
≤7	234/893 (26%)	269/811 (33%)	0·76 (0·64–0·91)
>7	161/739 (22%)	183/709 (26%)	0·83 (0·67–1·03)
Respiratory support received (χ^2_1=0·4; p=0·55)			
No oxygen received	23/182 (13%)	29/148 (20%)	0·63 (0·36–1·09)
Simple oxygen	221/1085 (20%)	247/995 (25%)	0·81 (0·67–0·97)
Non-invasive ventilation	139/332 (42%)	159/341 (47%)	0·86 (0·68–1·08)
Invasive mechanical ventilation	13/34 (38%)	17/36 (47%)	0·71 (0·35–1·47)
Use of corticosteroids (χ^2_1=4·0; p=0·05)			
Yes	378/1481 (26%)	423/1399 (30%)	0·83 (0·72–0·95)
No	18/152 (12%)	29/118 (25%)	0·45 (0·25–0·80)
All participants	**396/1633 (24%)**	**452/1520 (30%)**	**0·79 (0·69–0·91)**

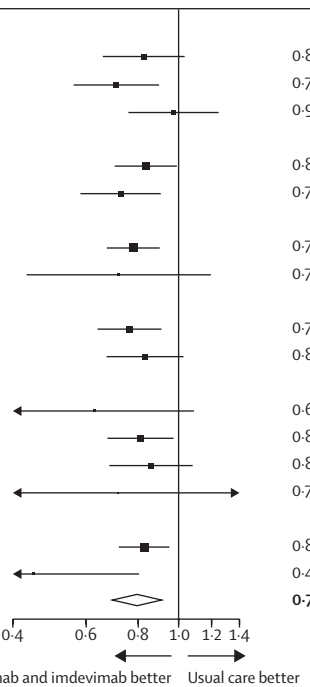

Figure 4: **Effect of allocation to casirivimab and imdevimab on 28-day mortality by baseline characteristics in seronegative patients**
Subgroup-specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. The ethnicity, days since onset, and use of corticosteroids subgroups exclude patients with missing data, but these patients are included in the overall summary diamond. RR=rate ratio. χ^2_1=test for heterogeneity or trend.

COVID-19 were all terminated early based on interim futility analyses.[25,26] Although there was some evidence of potential heterogeneity of effect of BRII-196 with BRII-198 by baseline serostatus, none of these three evaluations were powered to detect moderate treatment effects in subgroups defined by baseline serostatus. The total number of patients enrolled in these three evaluations was 860, less than 10% of the number enrolled in the RECOVERY evaluation of casirivimab and imdevimab.

Based on our findings, any therapeutic use of casirivimab and imdevimab combination in the hospital setting would be best restricted to seronegative patients, as has now been implemented in the UK based on our results.[36] This approach requires serological testing before drug administration. High-performance, laboratory-based commercial assays for anti-SARS-CoV-2 antibodies are available and used in high-income health-care settings. For example, we noted similar results when analyses of the primary and secondary outcomes were repeated using a commercially available assay for either anti-spike or anti-nucleocapsid antibodies. However, serology assays are not widely available in lower-income settings.[37] Point-of-care lateral-flow immunoassays have been developed but some have suboptimal performance and their suitability for guiding therapeutic decisions, as opposed to sero-epidemiological studies, requires further evaluation.[34,38,39] Assays with lower costs and technological requirements than commercial bench-top systems and better performance than lateral-flow immunoassays have been developed and might offer more scalable and affordable options for serostatus evaluation but these also require further evaluation before clinical use.[40]

This study was conducted predominantly at a time before the widespread use of SARS-CoV-2 vaccines, when serostatus (the presence of antibodies to the viral spike protein) was reflective of acute response to infection. Now, however, seropositive status might additionally reflect the response to previous SARS-CoV-2 vaccination rather than acute infection. The vaccine-induced antibody response might be quantitatively and qualitatively different to the virus-induced antibody response. Although serological testing strategies, such as testing for antibodies against both spike and nucleocapsid proteins, might help to distinguish between vaccine-induced versus acute virus-induced antibody responses, it is not known if casirivimab and imdevimab treatment would be beneficial in vaccinated patients with COVID-19 who are S-antibody positive but N-antibody negative. The reliability of seropositive status as a predictor of therapeutic non-response to monoclonal antibodies is further complicated by the emergence of the B.1.1.529

variant (omicron) that can evade antibodies raised against earlier SARS-CoV-2 variants. Going forward, antigen status might be a more meaningful biomarker of potential therapeutic response to monoclonal antibodies than antibody status.[26]

In October, 2020, the independent data monitoring committee of an industry-sponsored trial[41] of casirivimab and imdevimab in patients with COVID-19 admitted to hospital recommended that recruitment of patients on high-flow oxygen or mechanical ventilation be suspended because of a potential safety signal, while an interim analysis of the same trial in December, 2020, suggested a possible benefit in patients on low-flow oxygen.[20] However, we did not observe any evidence that the proportional effect of casirivimab and imdevimab on mortality varied by level of respiratory support received at randomisation, either when assessed in all participants or when assessed only in the subgroup of seronegative participants.

Monoclonal antibodies are susceptible to the evolution of viral resistance if substitutions in the targeted epitope reduce or abrogate antibody binding, and a US Emergency Use Authorisation for monotherapy with the monoclonal antibody LY-CoV555 was revoked because of resistance in several major virus variants.[42] This risk can be reduced by using a combination of monoclonal antibodies that bind to non-overlapping epitopes.[14] Although we did not study the emergence of resistance variants in this trial, the major variants circulating in the UK throughout the trial, including the B.1.1.7 (alpha) variant that was the dominant variant in the UK from December, 2020, to April, 2021, remained sensitive to casirivimab and imdevimab.[43-46] Although spike glycoprotein mutations at residue E484 of the spike glycoprotein in some variants (eg, B.1.351 [beta, E484K], and B.1.617.1 [kappa, E484Q]) are associated with a marked reduction of neutralisation activity of casirivimab, the combination of casirivimab with imdevimab retains potency against these variants because of the inhibitory activity of imdevimab.[43–45,47] Although the B.1.617.2 (delta) variant is associated with markedly reduced neutralisation activity of imdevimab, the neutralising activity of casirivimab is retained, such that the combination likely retains clinical effectiveness against the delta variant.[46,48] In late 2021, after this study of casirivimab and imdevimab was completed, the omicron variant of SARS-CoV-2 emerged. With numerous amino acid substitutions in the spike glycoprotein, omicron is able to evade neutralisation by some naturally occurring, vaccine-induced and monoclonal antibodies. Both casirivimab and imdevimab have markedly reduced ability to neutralise omicron in vitro and, therefore, are unlikely to retain clinical effectiveness against the omicron variant. However, this study is proof of principle that monoclonal antibody therapy can have clinical benefit in hospitalised patients with COVID-19. The emergence of the omicron variant highlights the importance of continued monitoring of resistance, the ongoing development and evaluation of monoclonal antibody preparations that are not sensitive to common and newly arising substitutions, and the exploration of antiviral combination therapies with different mechanisms of action.[49]

The strengths of this trial included that it was randomised, had a large sample size, broad eligibility criteria, and more than 99% of patients were followed up for the primary outcome. The study has some limitations: information on virological outcomes was not collected, nor was information on radiological or physiological outcomes. Although this randomised trial is open label (ie, participants and local hospital staff are aware of the assigned treatment), the outcomes are unambiguous and were ascertained without bias through linkage to routine health records. The dose of casirivimab and imdevimab used in this study was high compared to those used in outpatient studies; understanding the effects of lower doses would require additional evidence from a randomised controlled trial.[16]

In summary, this large, randomised trial provides the first evidence that an antiviral therapy can reduce mortality in patients admitted to hospital with COVID-19. The results support the use of the monoclonal neutralising antibody combination of casirivimab and imdevimab in seronegative patients admitted to hospital with COVID-19 caused by SARS-CoV-2 variants that are sensitive to these antibodies.

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This manuscript was initially drafted by PWH and MJL, further developed by the Writing Committee, and approved by all members of the trial steering committee. PWH and MJL approved the data and analyses, and vouch for the fidelity of this report to the study protocol and data analysis plan. PWH, MM, JKB, MHB, LCC, JD, SNF, TJ, EJ, KJ, WSL, AMo, AMu, KR, RH, and MJL designed the trial and study protocol. MM, LP, MC, GP-A, BP, PH, TBr, CAG, RS, PD, BY, TBe, ST, TF, and the Data Linkage team at the RECOVERY Coordinating Centre, and the Health Records and Local Clinical Centre staff listed in the appendix collected the data. ES, NS, and JRE did the statistical analysis. All authors contributed to data interpretation, and critical review and revision of the manuscript. PWH and MJL (the corresponding authors) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
DMW is an employee of Regeneron Pharmaceuticals and holds shares or share options in the company. All other authors declare no competing

interests or financial relationships relevant to the submitted work. No form of payment was given to anyone to produce the manuscript. The Nuffield Department of Population Health at the University of Oxford has a staff policy of not accepting honoraria or consultancy fees directly or indirectly from industry (see https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf).

Data sharing

The protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online. As described in the protocol, the trial steering committee will facilitate the use of the study data and approval will not be unreasonably withheld. Deidentified participant data will be made available to researchers registered with an appropriate institution within 3 months of publication. However, the steering committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures described at: https://www.ndph.ox.ac.uk/data-access. Individuals wishing to request access should complete the form at https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx and e-mail to: data.access@ndph.ox.ac.uk.

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