

REGEN-COV for COVID-19

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

Running title: REGEN-COV for COVID-19

RECOVERY Collaborative Group*

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the Supplementary Appendix.

Correspondence to: Prof Peter W Horby and Prof Martin J Landray, RECOVERY Central Coordinating Office, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom.

Email: recoverytrial@ndph.ox.ac.uk

REGEN-COV for COVID-19

SUMMARY

Background: REGEN-COV is a combination of 2 monoclonal antibodies (casirivimab and imdevimab) that bind to two different sites on the receptor binding domain of the SARS-CoV-2 spike protein. We aimed to evaluate the efficacy and safety of REGEN-COV in patients admitted to hospital with COVID-19.

Methods: In this randomised, controlled, open-label platform trial, several possible treatments were compared with usual care in patients hospitalised with COVID-19. Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus a single dose of REGEN-COV 8g (casirivimab 4g and imdevimab 4g) by intravenous infusion (REGEN-COV group). The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population. The trial is registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

Findings: Between 18 September 2020 and 22 May 2021, 9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status. In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0·80; 95% CI 0·70-0·91; $p=0\cdot0010$). In an analysis involving all randomised patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (rate ratio 0·94; 95% CI 0·86-

REGEN-COV for COVID-19

46 1·03; $p=0\cdot17$). The proportional effect of REGEN-COV on mortality differed significantly
47 between seropositive and seronegative patients (p value for heterogeneity = $0\cdot001$).

48 **Interpretation:** In patients hospitalised with COVID-19, the monoclonal antibody
49 combination of casirivimab and imdevimab (REGEN-COV) reduced 28-day mortality
50 among patients who were seronegative at baseline.

51 **Funding:** UK Research and Innovation (Medical Research Council) and National Institute
52 of Health Research (Grant ref: MC_PC_19056).

53 **Keywords:** COVID-19, monoclonal antibodies, spike protein, clinical trial.

54

REGEN-COV for COVID-19

INTRODUCTION

Monoclonal antibodies (mAbs) are a set of identical antibodies that have high specificity and affinity for a single epitope. They have been demonstrated 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 mAbs in viral infections is thought to be mediated through direct binding to free virus particles and neutralisation of their ability to infect host cells. mAbs may also bind to viral antigens expressed on the surface of infected cells and stimulate antibody-dependent phagocytosis and cytotoxicity via the Fc portion of the mAb.⁴

SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike glycoprotein to angiotensin converting enzyme 2 (ACE2) on the surface of host cells.⁵ The receptor binding domain of the spike glycoprotein is, consequently, the main target for neutralising antibodies.⁶ Following the emergence of SARS-COV-2, mAbs 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 neutralizing mAbs have demonstrated in vivo efficacy in both therapeutic and prophylactic settings in mouse, and non-human primates models, with decreases in viral load and lung pathology.⁹⁻¹²

Regeneron Pharmaceuticals (Tarrytown, New York, USA) has developed two non-competing, high-affinity human IgG1 anti-SARS-CoV-2 mAbs, casirivimab and imdevimab, 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

REGEN-COV for COVID-19

antibodies that bind to non-overlapping epitopes, rather than a single antibody, is intended to minimize 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 non-hospitalised adults with SARS-COV-2 infection and risk factors for severe COVID-19, the combination of casirivimab and imdevimab (REGEN-COV) was safe and, compared to placebo, reduced virus load in the upper airway, shortened the time to symptom resolution, and reduced the composite outcome of COVID-19-related hospitalisation or all-cause mortality.^{15,16} Other anti-spike mAb products have also demonstrated an antiviral and clinical effect in non-hospitalised adults with SARS-COV-2 infection.^{17,18} In the United States, Emergency Use Authorization has been given for the use of bamlanivimab with etesevimab, REGEN-COV, and sotrovimab in non-hospitalised patients with mild to moderate COVID-19. The European Medicines Agency has authorised REGEN-COV 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 of REGEN-COV in hospitalised patients requiring low-flow oxygen was consistent with a clinical benefit in seronegative patients.¹⁹

However, to date, no virus-directed therapy has been shown to reduce mortality in hospitalised patients with COVID-19, for whom the only treatments so far shown to reduce mortality have been those that modify the inflammatory response.²⁰⁻²² The only published trial of an anti-spike mAb (bamlanivimab) in hospitalised patients was terminated for futility after 314 patients had been randomised.^{23,24} Two other studies of mAb products (VIR-7831 monotherapy, and BRII-196 with BRII-198 combination therapy) in hospitalized COVID-19 patients were also terminated for futility with sample sizes of 344

REGEN-COV for COVID-19

and 343 respectively.²⁵ On first principles, the clinical response to antibody-based therapies may be greatest in individuals early in disease or who fail to mount an effective immune response. This is supported by evidence of clinical benefit in early disease and evidence that baseline anti-SARS-CoV-2 antibody status may be an important predictor of the effect of anti-spike mAbs on viral load.^{15,16,19} A significant proportion of hospitalised COVID-19 patients are seronegative on admission, and although a greater proportion already have detectable anti-SARS-CoV-2 antibodies, the quality of their immunological response may be poor since it has failed to prevent disease progression.²⁶ As such, anti-spike mAbs may have benefit even in later COVID-19 disease. Here we report the results of a large randomised controlled trial of REGEN-COV in patients hospitalised 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 to evaluate the effects of potential treatments in patients hospitalised 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.^{20,21,26-30} The trial is underway at 177 hospitals in the United Kingdom supported by the National Institute for Health Research Clinical Research Network, two hospitals in Indonesia, and two hospitals in Nepal (appendix pp

REGEN-COV for COVID-19

3-27). Of these, 127 UK hospitals took part in the evaluation of REGEN-COV. The trial is 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 available in the appendix (pp 68-148) with additional information available on the study website www.recoverytrial.net.

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 REGEN-COV. Pregnant or breastfeeding women were eligible for inclusion. Written informed consent was obtained from all patients, or a legal representative if patients were too unwell or unable to provide consent.

Randomisation and masking

Baseline data were collected using a web-based case report form that included demographics, 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).

REGEN-COV for COVID-19

Baseline presence of anti-SARS-CoV-2 antibodies was to be determined for each participant using serum samples taken at the time of randomisation. Analysis was done at a central laboratory with a validated 384 well plate indirect ELISA for anti-spike IgG (appendix p 28).³¹ 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.³¹

Eligible and consenting patients were assigned in a 1:1:1 ratio to either usual standard of care, usual standard of care plus REGEN-COV or usual standard of care plus convalescent plasma (until 15 January 2021), using web-based simple (unstratified) randomisation with allocation concealed until after randomisation (appendix pp 32-33). For some patients, REGEN-COV 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 REGEN-COV and usual care. Patients allocated to REGEN-COV were to receive a single dose of REGEN-COV 8g (casirivimab 4g and imdevimab 4g) in 250ml 0.9% saline infused intravenously over 60 minutes +/- 15 minutes as soon as possible after randomisation.

As a platform trial, and in a factorial design, patients could be simultaneously randomised to other treatment groups: i) azithromycin versus usual care, ii) colchicine versus usual care, iii) aspirin versus usual care, and iv) baricitinib versus usual care. Further details of when these factorial randomisations were open is provided in the supplementary appendix (pp 32-33). Until 24 January 2021, the trial also allowed a subsequent randomisation for patients with progressive COVID-19 (evidence of hypoxia and a hyper-inflammatory state) to tocilizumab versus usual care. Participants and local study staff

REGEN-COV for COVID-19

were not masked to the allocated treatment. The trial steering committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.

Procedures

Early safety outcomes were recorded by site staff using an online form 72 hours 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, routine 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, among patients not on invasive mechanical ventilation at randomisation, the composite outcome of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death. Prespecified 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 dialysis or haemofiltration. Information on suspected serious

REGEN-COV for COVID-19

adverse reactions was collected in an expedited fashion to comply with regulatory requirements. Details of the methods used to ascertain and derive outcomes are provided in the appendix (pp.149-169).

Prespecified safety outcomes were cause-specific mortality, major cardiac arrhythmia, and thrombotic and major bleeding events (only collected since 6 November 2021). Information on early safety outcomes at 72 h following randomisation (worsening respiratory status, severe allergic reactions, fever, sudden hypotension, clinical haemolysis, and thrombotic events) ceased on 19 February 2021 on the advice of the Data Monitoring Committee and in accordance with the protocol.

Statistical Analysis

For all outcomes, intention-to-treat analyses compared patients randomised to REGEN-COV with patients randomised to usual care but for whom REGEN-COV 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 (i.e., the log-rank test) and to calculate the one-step estimate of the average mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period.

For this preliminary report, information on the primary outcome is available for 99% of randomised patients. Those patients who had not been followed for 28 days and were not known to have died by the time of the data cut for this preliminary analysis (25 May 2021) were either censored on 25 May 2021 or, if they had already been discharged alive, were right-censored for mortality at day 29 (that is, in the absence of any information to the

REGEN-COV for COVID-19

210 contrary they were assumed to have survived 28 days). [Note: This censoring rule will not
211 be necessary when all patients have completed the 28 day follow-up period on 19 June
212 2021.]

213 We used the same method to analyse time to hospital discharge and successful cessation
214 of invasive mechanical ventilation, with patients who died in hospital right-censored on
215 day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the pre-
216 specified composite secondary outcome of progression to invasive mechanical ventilation
217 or death within 28 days (among those not receiving invasive mechanical ventilation at
218 randomisation), and the subsidiary clinical outcomes of receipt of ventilation and use of
219 haemodialysis or haemofiltration, the precise dates were not available and so the risk
220 ratio was estimated instead. Estimates of rate and risk ratios (both denoted RR) are
221 shown with 95% confidence intervals.

222 In the light of new evidence which became available during the trial, it was hypothesised
223 that any beneficial effect of REGEN-COV would be larger among seronegative
224 participants (and may be negligible in seropositive participants).^{15,19} Consequently, prior
225 to any unblinding of results, the trial steering committee specified that hypothesis-testing
226 of the effect of allocation to REGEN-COV on 28-day mortality (and secondary outcomes)
227 would first be done only in seronegative participants (appendix pp. 142-144). Hypothesis
228 testing of the primary outcome among all randomised patients was then only to be done
229 if a reduction in mortality in seronegative patients was seen at $2P < 0.05$. A prespecified
230 comparison of the effects of allocation to REGEN-COV on 28-day mortality in
231 seronegative versus seropositive participants was done by performing a test for
232 heterogeneity. Tests for heterogeneity according to other baseline characteristics (age,

REGEN-COV for COVID-19

233 sex, ethnicity, level of respiratory support, days since symptom onset, and use of
234 corticosteroids) (appendix p 133-134) were also prespecified.

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

238 As stated in the protocol, appropriate sample sizes could not be estimated when the trial
239 was being planned at the start of the COVID-19 pandemic. On 27 April 2021, the trial
240 steering committee, whose members were unaware of the results of the trial comparisons,
241 determined that, with over 9700 patients recruited to the REGEN-COV comparison and
242 average daily recruitment of 4 patients, further recruitment was unlikely to increase
243 reliability of the results materially so should discontinue (appendix p 33-34). The statistical
244 analysis plan was finalised and published on 21 May 2021 (without any knowledge of the
245 study results) (appendix pp 112-148) and recruitment to the REGEN-COV comparison
246 was closed on 22 May 2021. The trial steering committee and all other individuals involved
247 in the trial were masked to outcome data until after the close of recruitment (appendix p
248 49).

249 Analyses were performed using SAS version 9.4 and R version 4.0.3. The trial is
250 registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

251 **Role of the funding source**

252 The funder of the study had no role in study design, data collection, data analysis, data
253 interpretation, or writing of the report. Regeneron Pharmaceuticals supported the study

REGEN-COV for COVID-19

through supply of REGEN-COV and provided comments on the manuscript for consideration by the writing committee but had no role in the decision to submit for publication. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between 18 September 2020 and 22 May 2021, 11464 (47%) of 24343 patients enrolled into the RECOVERY trial at one of the 127 sites were eligible to be randomly allocated to REGEN-COV (i.e. REGEN-COV 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 REGEN-COV, figure 1). 4839 patients were randomly allocated to REGEN-COV and 4946 were randomly allocated 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 to 12 days) (webtable 1). At randomisation, 9169 (94%) patients were receiving corticosteroids. 5272 (54%) were seropositive at baseline, 3153 (32%) were seronegative, and serostatus was unknown for 1360 (14%) (table 1, webtables 1 and 2).

The follow-up form was completed for 4773 (99%) in the REGEN-COV group and 4899 (99%) in the usual care group. Among patients with a completed follow-up form, 90% allocated to REGEN-COV received the treatment compared with <1% allocated to usual care (figure 1). Use of other treatments for COVID-19 was similar among patients allocated REGEN-COV and among those allocated usual care, with about one-quarter

REGEN-COV for COVID-19

receiving remdesivir and one-seventh receiving tocilizumab (webtable 3). Primary and secondary outcome data are known for 99% of randomly assigned patients.

Among patients who were known to be seronegative at baseline, allocation to REGEN-COV 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 REGEN-COV group died vs 451 (30%) of 1520 patients in the usual care group (rate ratio 0.80; 95% CI, 0.70–0.91; $p=0.0010$; table 2, figure 2a, and figure 3). The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (test for heterogeneity $p=0.001$; figure 3). Among all patients randomised (including those with negative, positive, or unknown baseline antibody status), there was no significant difference in the primary outcome of 28-day mortality between the two randomised groups: 944 (20%) of 4839 patients in the REGEN-COV group died vs. 1026 (21%) of 4946 patients in the usual care group (rate ratio 0.94; 95% CI, 0.86 to 1.03; $p=0.17$; webtable 4, figure 2b, and figure 3).

In both the seronegative patients and in all patients combined, the proportional effects on mortality seen in the respective populations were consistent across all other pre-specified subgroups (webfigure 1 and webfigure 2). Results were virtually identical when restricted to participants with a positive SARS-CoV-2 PCR test (webtable 5). In a sensitivity analysis using a Cox model adjusted for all pre-specified subgroups, allocation to REGEN-COV was associated with a mortality rate ratio of 0.85 (95% CI 0.74-0.98) in seronegative patients (webtable 5). Among all participants, there was no evidence that the effect on mortality varied depending on concurrent randomised allocation to azithromycin, colchicine, or aspirin (all interaction p -values >0.1).

REGEN-COV for COVID-19

Among seronegative patients, discharge alive within 28 days was more common among those allocated to REGEN-COV compared with usual care (64% vs. 58%; rate ratio 1.19, 95% CI 1.08 to 1.30; median 13 days [IQR 7 to >28] vs. 17 days [IQR 7 to >28]) (table 2, figure 3 and webfigure 3a). However, there was no meaningful difference among the overall study population (70% vs. 69%; rate ratio 1.01, 95% CI 0.97 to 1.07; median 10 days [IQR 6 to >28] vs. 10 days [IQR 5 to >28]) (webtable 4, figure 3 and webfigure 3b).

Among seronegative patients not on invasive mechanical ventilation at baseline, allocation to REGEN-COV was associated with a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (30% vs. 37%, risk ratio 0.83, 95% CI 0.75 to 0.92) (table 2 and figure 3). However, there was no difference among the overall study population (24% vs. 25%, risk ratio 0.96, 95% CI 0.90 to 1.04) (webtable 4 and figure 3).

There was clear evidence that the proportional effects on each of these secondary outcomes differed significantly between seropositive and seronegative patients (p value for heterogeneity both <0.001) (figure 3). There was no good evidence of differences in treatment effect in other subgroups of patients (webfigures 4 and 5).

Among seronegative patients, allocation to REGEN-COV versus usual care was associated with less frequent progression to use of ventilation among patients not on such treatment at baseline versus usual care (28% vs 32%; risk ratio 0.87, 95% CI 0.77 to 0.98) (table 2) but not in the overall study population (23% vs. 24%; risk ratio 0.95, 95% CI 0.87 to 1.04) (webtable 4). There were no meaningful differences in progression to renal replacement therapy, non-COVID mortality, cardiac arrhythmia, thrombosis or major

REGEN-COV for COVID-19

bleeding either in the seronegative or overall study populations (table 2, webtables 4, 6, 7 and 8).

Information on potential infusion reactions occurring within the first 72 hours after randomisation was collected for 1792 patients in the REGEN-COV group and 1714 patients in the usual care group (before collection of these data stopped on 19 February 2021): The reported frequency of fever (4% vs. 3%), sudden hypotension (4% vs. 2%), and thrombotic events (2% vs. 1%) was marginally higher in the REGEN-COV group vs. the usual care group while the frequency of sudden worsening in respiratory status (21% vs. 22%) and clinical haemolysis (1% vs. 2%) was marginally lower (webtable 9). There were 5 reports of a serious adverse reaction believed to be related to REGEN-COV (webtable 10).

332

DISCUSSION

In this large, randomised trial, allocation to REGEN-COV in patients who were anti-SARS-CoV-2 antibody negative at randomisation significantly reduced 28-day mortality by about one-fifth, an absolute benefit of 6 fewer deaths per 100 patients allocated REGEN-COV. In addition, allocation to REGEN-COV 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), allocation to REGEN-COV was associated with non-significant

REGEN-COV for COVID-19

differences in clinical outcomes. Only one other trial has reported the effects of an anti-spike mAb in hospitalised COVID-19 patients, and this trial was terminated for futility based on clinical status at day 5 in 314 patients.²³ However, the result were not reported by baseline serostatus and that trial was underpowered to detect moderate effects in subgroups. Whilst two other trials of mAbs in hospitalised patients were also terminated for futility by the same group, full details are not yet published.²⁵

Based on our findings, any therapeutic use of REGEN-COV in the hospital setting may be best restricted to seronegative patients. This would require serological testing prior to drug administration. High-performance, laboratory-based commercial assays for SARS-CoV-2 antibodies are available and used in high-income healthcare settings. However, they are not widely available in lower income settings.³² 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.^{31,33,34} Assays with lower costs and technological requirements than commercial bench-top systems and better performance than lateral-flow immunoassays have been developed and may offer more scalable and affordable options for serostatus evaluation but these also require further evaluation before clinical use.³⁵

In October 2020 the independent data monitoring committee of an industry sponsored trial of REGEN-COV in hospitalised COVID-19 patients recommended that recruitment of patients on high-flow oxygen or mechanical ventilation be suspended because of a potential safety signal.³⁶ However, we did not observe any evidence that the proportional effect of REGEN-COV on mortality varied by level of respiratory support received at

REGEN-COV for COVID-19

randomisation, either when assessed in all participants or when assessed only in the sub-group of seronegative participants.

mAbs are susceptible to the evolution of viral resistance if substitutions in the targeted epitope reduce or abrogate antibody binding, and an Emergency Use Authorisation for monotherapy with the mAb LY-CoV555 was revoked due to resistance in several major virus variants.³⁷ This risk can be reduced by using a combination of mAbs that bind to non-overlapping epitopes.¹⁴ Whilst we did not study the emergence of resistance variants in this trial, the major variants circulating in the UK throughout the trial, including B.1.1.7 (alpha) variant which was the dominant variant in the UK from December 2020 to April 2021, remained sensitive to REGEN-COV.^{38,39} Although spike glycoprotein mutations in some variants (e.g. B.1.351 [beta] and B.1.617 [delta]) have been associated with a reduction of neutralisation activity of casirivimab, the combination of casirivimab with imdevimab retains potency against these variants due to the inhibitory activity of imdevimab.³⁸⁻⁴¹ However, continued monitoring of resistance patterns is imperative to detect variants with resistance to both components.

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. Information on virological outcomes was not collected, nor was information on radiological or physiological outcomes. Although this randomised trial is open label (i.e., 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 REGEN-COV used in this study was high compared to those used

REGEN-COV for COVID-19

387 in outpatient studies; understanding the effects of lower doses would require additional
388 evidence from a randomized controlled trial.¹⁶

389 In summary, this large, randomised trial provides the first evidence that an antiviral
390 therapy can reduce mortality in hospitalised COVID-19 patients and the results support
391 the use of REGEN-COV in seronegative patients hospitalised with COVID-19.

392

REGEN-COV for COVID-19

Contributors

This manuscript was initially drafted by the PWH and MJL, further developed by the Writing Committee, and approved by all members of the trial steering committee. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. PWH, MM JKB, MB, LCC, JD, SNF, TJ, EJ, KJ, WSL, AMo, AMu, KR, RH, and MJL designed the trial and study protocol. MM, LP, MC, G P-A, BP, PH, TB, CAG, RS, PD, BY, TB, 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 had access to the study data and had final responsibility for the decision to submit for publication.

Writing Committee (on behalf of the RECOVERY Collaborative Group):

Peter W Horby,* Marion Mafham,* Leon Peto, Mark Campbell, Guilherme Pessoa-Amorim, Enti Spata, Natalie Staplin, Jonathan R Emberson, Benjamin Prudon, Paul Hine, Thomas Brown, Christopher A Green, Rahuldeb Sarkar, Purav Desai, Bryan Yates, Tom Bewick, Simon Tiberi, Tim Felton, J Kenneth Baillie, Maya H Buch, Lucy C Chappell, Jeremy Day, Saul N Faust, Thomas Jaki, Katie Jeffery, Edmund Juszczak, Wei Shen Lim, Alan Montgomery, Andrew Mumford, Kathryn Rowan, Guy Thwaites, David M Weinreich, Richard Haynes,⁺ Martin J Landray.⁺

* PWH and MM made an equal contribution

⁺ RH and MJL made an equal contribution

Data Monitoring Committee

Peter Sandercock, Janet Darbyshire, David DeMets, Robert Fowler, David Lalloo, Mohammed Munavvar (from January 2021), Ian Roberts (until December 2020), Adilia Warris (from March 2021), Janet Wittes.

REGEN-COV for COVID-19

Declaration of interests

DMW is an employee of Regeneron Pharmaceuticals and holds shares/share options in the company. All other authors have no conflict of interest or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to produce the manuscript. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. 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 & derivation of clinical characteristics & outcomes, training materials, regulatory documents, and other relevant study materials are available online at www.recoverytrial.net. 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 bona fide 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 (e.g. relating to data protection and privacy). The Steering Committee will have the right to review and comment on any draft manuscripts prior to publication. Data will be made available in line with the policy and procedures described at: <https://www.ndph.ox.ac.uk/data-access>. Those 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-mailed to: data.access@ndph.ox.ac.uk

REGEN-COV for COVID-19

Acknowledgements

Above all, we would like to thank the thousands of patients who participated in this trial. We would also like to thank the many doctors, nurses, pharmacists, other allied health professionals, and research administrators at 177 NHS hospital organisations across the whole of the UK, supported by staff at the National Institute of Health Research (NIHR) Clinical Research Network, NHS DigiTrials, Public Health England, Department of Health & Social Care, the Intensive Care National Audit & Research Centre, Public Health Scotland, National Records Service of Scotland, the Secure Anonymised Information Linkage (SAIL) at University of Swansea, NHS Blood & Transplant and the NHS in England, Scotland, Wales and Northern Ireland.

The RECOVERY trial is supported by grants to the University of Oxford from UK Research and Innovation (UKRI) and NIHR (MC_PC_19056), the Wellcome Trust (Grant Ref: 222406/Z/20/Z) through the COVID-19 Therapeutics Accelerator, and by core funding provided by the NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, the Foreign, Commonwealth and Development Office, Health Data Research UK, the Medical Research Council Population Health Research Unit, the NIHR Health Protection Unit in Emerging and Zoonotic Infections, and NIHR Clinical Trials Unit Support Funding. TJ is supported by a grant from UK Medical Research Council (MC_UU_00002/14) and an NIHR Senior Research Fellowship (NIHR-SRF-2015-08-001). WSL is supported by core funding provided by NIHR Nottingham Biomedical Research Centre. Tocilizumab was provided free of charge for this trial by Roche Products Limited. Regeneron Pharmaceuticals supported the trial through provision of REGEN-COV. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health and Social Care, or Regeneron Pharmaceuticals.

REGEN-COV for COVID-19

References

1. Laustsen AH. How can monoclonal antibodies be harnessed against neglected tropical diseases and other infectious diseases? *Expert Opin Drug Discov* 2019; **14**(11): 1103-12.
2. Mulangu S, Dodd LE, Davey RT, Jr., et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med* 2019; **381**(24): 2293-303.
3. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics* 1998; **102**(3): 531-7.
4. Winkler ES, Gilchuk P, Yu J, et al. Human neutralizing antibodies against SARS-CoV-2 require intact Fc effector functions for optimal therapeutic protection. *Cell* 2021; **184**(7): 1804-20 e16.
5. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veasler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**(2): 281-92 e6.
6. Ju B, Zhang Q, Ge J, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 2020; **584**(7819): 115-9.
7. Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun* 2020; **11**(1): 2251.
8. Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature* 2020; **583**(7815): 290-5.
9. Zost SJ, Gilchuk P, Case JB, et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature* 2020; **584**(7821): 443-9.
10. Shi R, Shan C, Duan X, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature* 2020; **584**(7819): 120-4.
11. Cao Y, Su B, Guo X, et al. Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells. *Cell* 2020; **182**(1): 73-84 e16.
12. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. *Science* 2020; **370**(6520): 1110-5.
13. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science* 2020.

REGEN-COV for COVID-19

- 508 14. Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike
509 protein prevents rapid mutational escape seen with individual antibodies. *Science* 2020;
510 **369**(6506): 1014-8.
- 511 15. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing
512 Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med* 2020.
- 513 16. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody
514 Cocktail Clinical Outcomes Study in Covid-19 Outpatients. *medRxiv* 2021:
515 2021.05.19.21257469.
- 516 17. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in
517 Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-
518 19: A Randomized Clinical Trial. *JAMA* 2021; **325**(7): 632-44.
- 519 18. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555
520 in Outpatients with Covid-19. *N Engl J Med* 2021; **384**(3): 229-37.
- 521 19. Regeneron. Regeneron announces encouraging initial data from covid-19
522 antibody cocktail trial in hospitalized patients on low-flow oxygen. 2020.
523 [https://investor.regeneron.com/news-releases/news-release-details/regeneron-](https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-initial-data-covid-19-antibody)
524 [announces-encouraging-initial-data-covid-19-antibody](https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-initial-data-covid-19-antibody) (accessed 31 May
525 2021).
- 526 20. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in
527 Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**(8): 693-704.
- 528 21. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital
529 with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.
530 *Lancet* 2021; **397**(10285): 1637-45.
- 531 22. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne
532 JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids
533 and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020;
534 **324**(13): 1330-41.
- 535 23. Activ-Tico Ly- CoV555 Study Group, Lundgren JD, Grund B, et al. A Neutralizing
536 Monoclonal Antibody for Hospitalized Patients with Covid-19. *N Engl J Med* 2021;
537 **384**(10): 905-14.
- 538 24. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-
539 19 - Final Report. *N Engl J Med* 2020; **383**(19): 1813-26.
- 540 25. National Institutes of Health. NIH-Sponsored ACTIV-3 Clinical Trial Closes
541 Enrollment into Two Sub-Studies. 2021. [https://www.nih.gov/news-events/news-](https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies)
542 [releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies](https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies)
543 (accessed 15 June 2021).

REGEN-COV for COVID-19

- 544 26. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to
545 hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform
546 trial. *Lancet* 2021.
- 547 27. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Lopinavir-
548 ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised,
549 controlled, open-label, platform trial. *Lancet* 2020; **396**(10259): 1345-52.
- 550 28. RECOVERY Collaborative Group, Horby P, Mafham M, et al. Effect of
551 Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020;
552 **383**(21): 2030-40.
- 553 29. RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital
554 with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.
555 *Lancet* 2021; **397**(10274): 605-12.
- 556 30. RECOVERY Collaborative Group, Horby PW, Campbell M, et al. Colchicine in
557 patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled,
558 open-label, platform trial. *medRxiv* 2021: 2021.05.18.21257267.
- 559 31. National Sars-CoV-Serology Assay Evaluation Group. Performance
560 characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark
561 comparison. *Lancet Infect Dis* 2020.
- 562 32. US Food and Drug Administration. EUA Authorized Serology Test Performance.
563 2021. [https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-](https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance)
564 [emergency-use-authorizations-medical-devices/eua-authorized-serology-test-](https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance)
565 [performance](https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance) (accessed 10 June 2021).
- 566 33. Moshe M, Daunt A, Flower B, et al. SARS-CoV-2 lateral flow assays for possible
567 use in national covid-19 seroprevalence surveys (React 2): diagnostic accuracy study.
568 *BMJ* 2021; **372**: n423.
- 569 34. Adams ER, Ainsworth M, Anand R, et al. Antibody testing for COVID-19: A report
570 from the National COVID Scientific Advisory Panel. *Wellcome Open Res* 2020; **5**: 139.
- 571 35. Townsend A, Rijal P, Xiao J, et al. A haemagglutination test for rapid detection of
572 antibodies to SARS-CoV-2. *Nat Commun* 2021; **12**(1): 1951.
- 573 36. Regeneron. Regn-cov2 independent data monitoring committee recommends
574 holding enrollment in hospitalized patients with high oxygen requirements and
575 continuing enrollment in patients with low or no oxygen requirements. 2020.
576 [https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-](https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends)
577 [independent-data-monitoring-committee-recommends](https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends) (accessed 01 June 2021).
- 578 37. Starr TN, Greaney AJ, Addetia A, et al. Prospective mapping of viral mutations
579 that escape antibodies used to treat COVID-19. *bioRxiv* 2020: 2020.11.30.405472.

REGEN-COV for COVID-19

- 580 38. Wang P, Nair MS, Liu L, et al. Increased Resistance of SARS-CoV-2 Variants
581 B.1.351 and B.1.1.7 to Antibody Neutralization. *bioRxiv* 2021.
- 582 39. Diamond M, Chen R, Winkler E, et al. In vivo monoclonal antibody efficacy
583 against SARS-CoV-2 variant strains. *Res Sq* 2021.
- 584 40. Dejnirattisai W, Zhou D, Supasa P, et al. Antibody evasion by the Brazilian P.1
585 strain of SARS-CoV-2. *bioRxiv* 2021: 2021.03.12.435194.
- 586 41. Hoffmann M, Hofmann-Winkler H, Krüger N, et al. SARS-CoV-2 variant B.1.617
587 is resistant to Bamlanivimab and evades antibodies induced by infection and
588 vaccination. *bioRxiv* 2021: 2021.05.04.442663.
589

Table 1: Baseline characteristics (seronegative and all participants) by treatment allocation

	Seronegative patients		All patients	
	REGEN-COV (n=1633)	Usual Care (n=1520)	REGEN-COV (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 to 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	1324 (81)	1250 (82)	3768 (78)	3810 (77)
Black, Asian, and minority ethnic	147 (9)	136 (9)	588 (12)	696 (14)
Unknown	162 (10)	134 (9)	483 (10)	440 (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	935 (57)	913 (60)	2557 (53)	2662 (54)
SARS-CoV-2 PCR test result				
Positive	1580 (97)	1470 (97)	4680 (97)	4791 (97)
Negative	17 (1)	16 (1)	38 (1)	53 (1)
Unknown	36 (2)	34 (2)	121 (3)	102 (2)
Patient 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)
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 randomised 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)

Data are mean (SD), n (%), or median (IQR). *Includes 11 children (<18 years). † Includes 25 pregnant women. ‡ Defined as requiring ongoing specialist care. § Defined as estimated glomerular filtration rate <30 mL/min per 1.73 m²

Table 2: Effect of allocation to REGEN-COV on key study outcomes among seronegative participants

	REGEN-COV (n=1633)	Usual Care (n=1520)	RR (95% CI)
Primary outcome			
Mortality at 28 days	396 (24%)	451 (30%)	0.80 (0.70-0.91)
Secondary outcomes			
Median duration of hospitalisation, days	13 (7 to >28)	17 (7 to >28)	-
Discharged from hospital within 28 days	1046 (64%)	878 (58%)	1.19 (1.08-1.30)
Invasive mechanical ventilation or death*	487/1599 (30%)	542/1484 (37%)	0.83 (0.75-0.92)
Invasive mechanical ventilation	189/1599 (12%)	200/1484 (13%)	0.88 (0.73-1.06)
Death	383/1599 (24%)	434/1484 (29%)	0.82 (0.73-0.92)
Subsidiary outcomes			
Use of ventilation †	355/1267 (28%)	370/1143 (32%)	0.87 (0.77-0.98)
Non-invasive ventilation	341/1267 (27%)	360/1143 (31%)	0.85 (0.75-0.97)
Invasive mechanical ventilation	89/1267 (7%)	119/1143 (10%)	0.67 (0.52-0.88)
Successful cessation of invasive mechanical ventilation ‡	9/34 (26%)	12/36 (33%)	0.86 (0.36-2.03)
Renal replacement therapy §	68/1616 (4%)	64/1498 (4%)	0.98 (0.71-1.38)

Data are n (%), median (IQR) or n/N (%). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes.

* Analyses exclude those on invasive mechanical ventilation at randomisation.

† Analyses exclude those on invasive or non-invasive ventilation at randomisation.

‡ Analyses exclude those not receiving invasive mechanical ventilation at randomisation.

§ Analyses exclude those on renal replacement therapy at randomisation.

Figures

Figure 1: Trial profile

ITT=intention to treat. * Number recruited overall during period that adult participants could be recruited into REGEN-COV comparison. Of the 9785 randomised to REGEN-COV vs usual care, 4535 were additionally randomised to colchicine vs usual care (2238 [46%] of the REGEN-COV group vs 2297 [46%] of the usual care group); 5507 were additionally randomised to aspirin vs usual care (2665 [55%] of the REGEN-COV group vs 2842 [57%] of the usual care group), and 1772 patients were additionally randomised to baricitinib vs usual care (889 [18%] of the REGEN-COV group vs 883 [18%] of the usual care group). † Includes 185/4839 (4%) patients in the REGEN-COV arm and 271/4946 (5%) patients in the usual care arm allocated to tocilizumab.

Figure 2: Effect of allocation to REGEN-COV on 28-day mortality (a) in seronegative patients and seropositive patients (b) overall

Figure 3: Primary and secondary outcomes, overall and by baseline antibody status

Subgroup-specific rate ratio 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 tests for heterogeneity compare the log RRs in the seronegative versus seropositive subgroups (ie, ignoring those with unknown antibody status).

Figures

Figure 1: Trial profile

ITT=intention to treat. * Number recruited overall during period that adult participants could be recruited into REGEN-COV comparison. Of the 9785 randomised to REGEN-COV vs usual care, 4535 were additionally randomised to colchicine vs usual care (2238 [46%] of the REGEN-COV group vs 2297 [46%] of the usual care group); 5507 were additionally randomised to aspirin vs usual care (2665 [55%] of the REGEN-COV group vs 2842 [57%] of the usual care group), and 1772 patients were additionally randomised to baricitinib vs usual care (889 [18%] of the REGEN-COV group vs 883 [18%] of the usual care group). † Includes 185/4839 (4%) patients in the REGEN-COV arm and 271/4946 (5%) patients in the usual care arm allocated to tocilizumab.

Figure 2: Effect of allocation to REGEN-COV on 28-day mortality (a) in seronegative patients and seropositive patients (b) overall

Figure 3: Primary and secondary outcomes, overall and by baseline antibody status

Subgroup-specific rate ratio 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 tests for heterogeneity compare the log RRs in the seronegative versus seropositive subgroups (ie, ignoring those with unknown antibody status).

Figure 1: Trial profile – Flow of participants through the RECOVERY trial
 medRxiv preprint doi: <https://doi.org/10.1101/2021.06.15.21258542>; this version posted June 16, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a [CC-BY 4.0 International license](#).

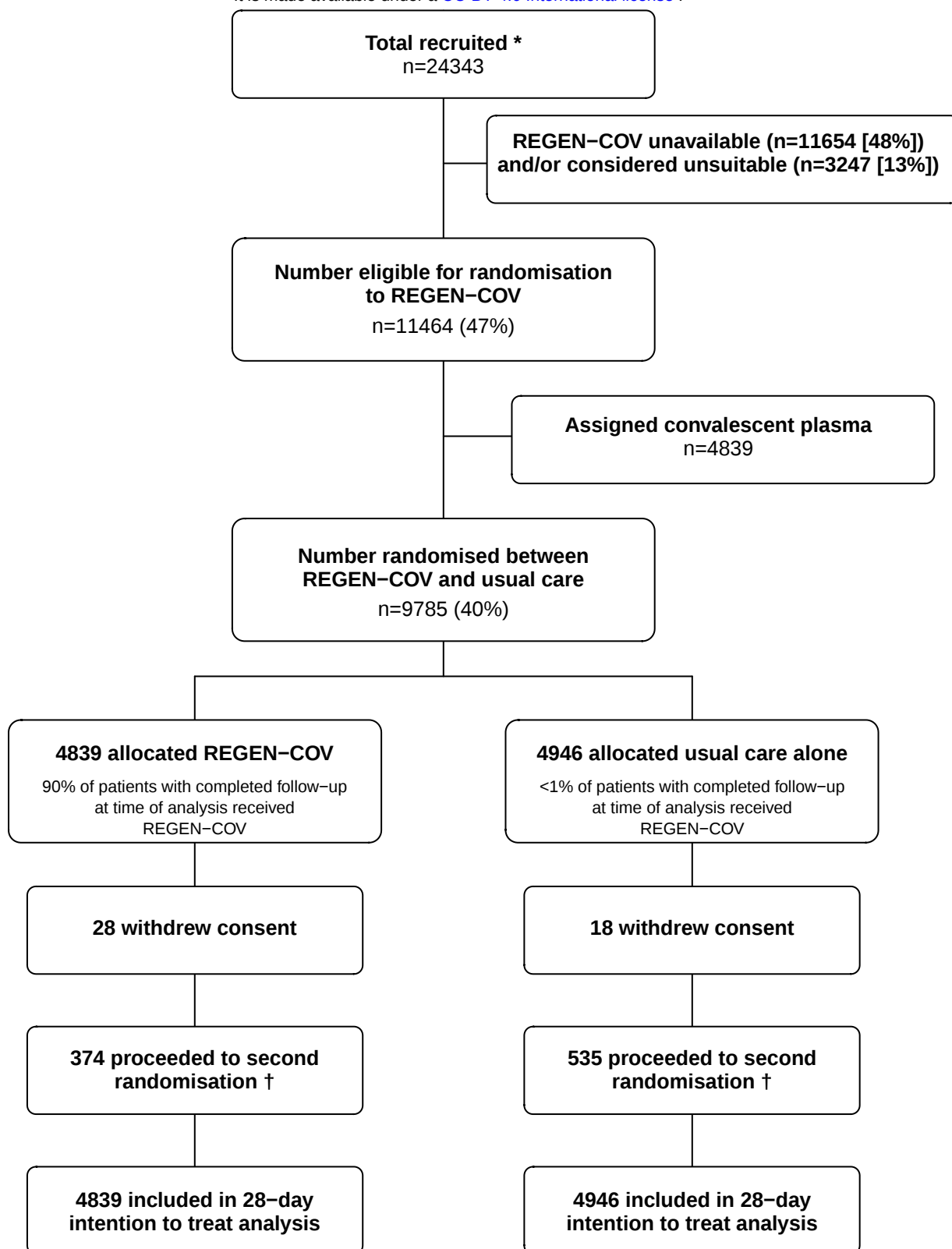


Figure 2: Effect of allocation to REGEN-COV on 28-day mortality in: a) seronegative vs seropositive participants; and b) all participants

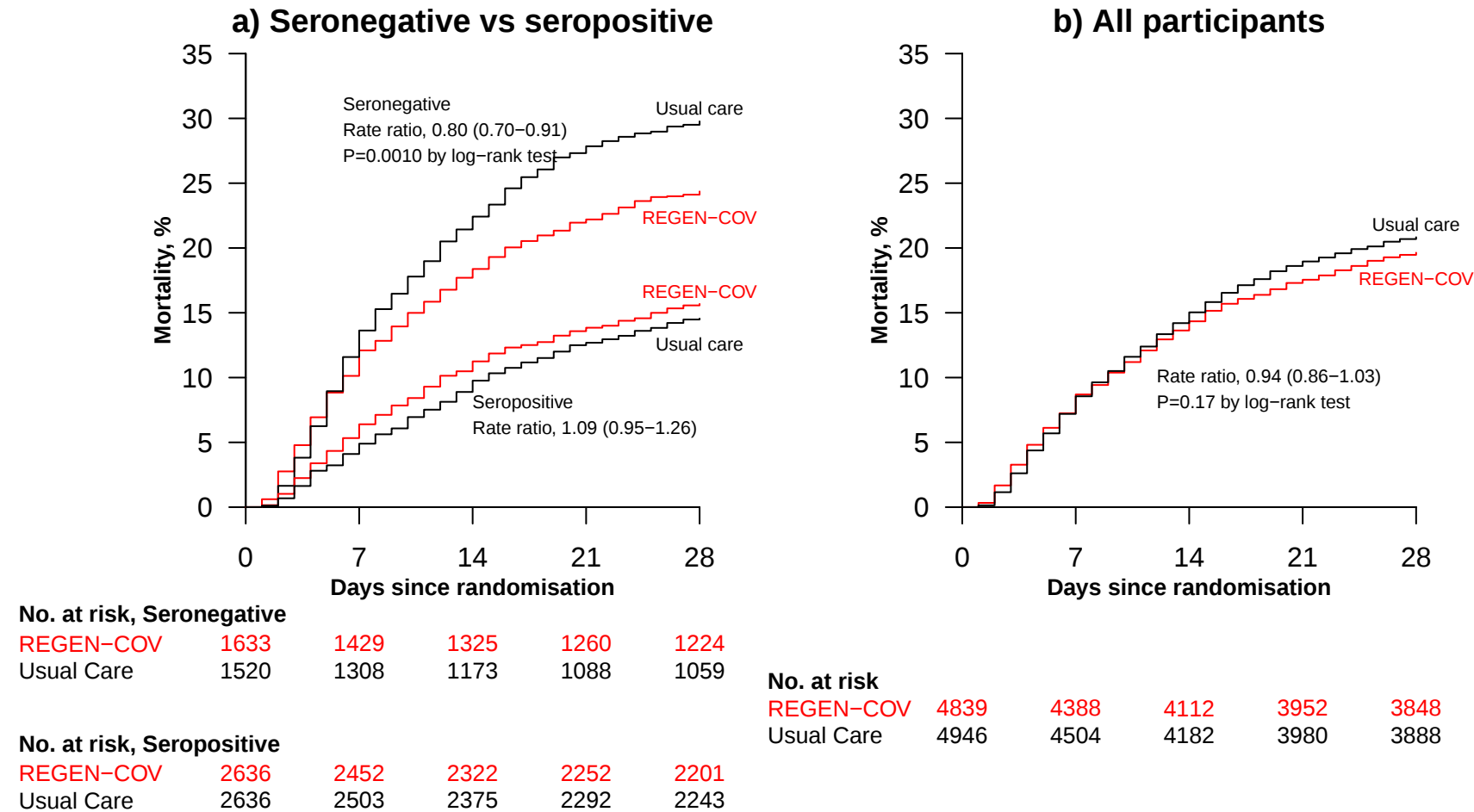


Figure 3: Primary and secondary outcomes, overall and by baseline antibody status

