

REGEN-COV for COVID-19

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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.

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23 SUMMARY

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

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

37 **Findings:** Between 18 September 2020 and 22 May 2021, 9785 patients were randomly
38 allocated to receive usual care plus REGEN-COV or usual care alone, including 3153
39 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients
40 with unknown baseline antibody status. In the primary efficacy population of seronegative
41 patients, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520
42 patients allocated to usual care died within 28 days (rate ratio 0.80; 95% CI 0.70-0.91;
43 $p=0.0010$). In an analysis involving all randomised patients (regardless of baseline
44 antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%)
45 of 4946 patients allocated to usual care died within 28 days (rate ratio 0.94; 95% CI 0.86-

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46 1.03; $p=0.17$). The proportional effect of REGEN-COV on mortality differed significantly
47 between seropositive and seronegative patients (p value for heterogeneity = 0.001).

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

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55 INTRODUCTION

56 Monoclonal antibodies (mAbs) are a set of identical antibodies that have high specificity
57 and affinity for a single epitope. They have been demonstrated to be safe and effective in
58 selected viral diseases when used for prophylaxis (respiratory syncytial virus) or
59 treatment (Ebola virus disease).¹⁻³ The clinical efficacy of mAbs in viral infections is
60 thought to be mediated through direct binding to free virus particles and neutralisation of
61 their ability to infect host cells. mAbs may also bind to viral antigens expressed on the
62 surface of infected cells and stimulate antibody-dependent phagocytosis and cytotoxicity
63 via the Fc portion of the mAb.⁴

64 SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike
65 glycoprotein to angiotensin converting enzyme 2 (ACE2) on the surface of host cells.⁵
66 The receptor binding domain of the spike glycoprotein is, consequently, the main target
67 for neutralising antibodies.⁶ Following the emergence of SARS-COV-2, mAbs targeting
68 the spike receptor binding domain were rapidly isolated from humanised mice and from
69 peripheral B cells of recovered patients.^{7,8} Anti-SARS-CoV-2 spike protein neutralizing
70 mAbs have demonstrated in vivo efficacy in both therapeutic and prophylactic settings in
71 mouse, and non-human primates models, with decreases in viral load and lung
72 pathology.⁹⁻¹²

73 Regeneron Pharmaceuticals (Tarrytown, New York, USA) has developed two non-
74 competing, high-affinity human IgG1 anti-SARS-CoV-2 mAbs, casirivimab and
75 imdevimab, which bind specifically to the receptor binding domain of the spike
76 glycoprotein of SARS-CoV-2, blocking viral entry into host cells.¹³ A combination of

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77 antibodies that bind to non-overlapping epitopes, rather than a single antibody, is
78 intended to minimize the likelihood of loss of antiviral activity due to naturally circulating
79 viral variants or development of escape mutants under drug pressure.¹⁴ In a clinical study
80 in non-hospitalised adults with SARS-COV-2 infection and risk factors for severe COVID-
81 19, the combination of casirivimab and imdevimab (REGEN-COV) was safe and,
82 compared to placebo, reduced virus load in the upper airway, shortened the time to
83 symptom resolution, and reduced the composite outcome of COVID-19-related
84 hospitalisation or all-cause mortality.^{15,16} Other anti-spike mAb products have also
85 demonstrated an antiviral and clinical effect in non-hospitalised adults with SARS-COV-
86 2 infection.^{17,18} In the United States, Emergency Use Authorization has been given for the
87 use of bamlanivimab with etesevimab, REGEN-COV, and sotrovimab in non-hospitalised
88 patients with mild to moderate COVID-19. The European Medicines Agency has
89 authorised REGEN-COV for use in patients who are at high risk of progressing to severe
90 COVID-19 but do not require supplemental oxygen. Interim results from a small trial of
91 REGEN-COV in hospitalised patients requiring low-flow oxygen was consistent with a
92 clinical benefit in seronegative patients.¹⁹

93 However, to date, no virus-directed therapy has been shown to reduce mortality in
94 hospitalised patients with COVID-19, for whom the only treatments so far shown to reduce
95 mortality have been those that modify the inflammatory response.²⁰⁻²² The only published
96 trial of an anti-spike mAb (bamlanivimab) in hospitalised patients was terminated for
97 futility after 314 patients had been randomised.^{23,24} Two other studies of mAb products
98 (VIR-7831 monotherapy, and BR11-196 with BR11-198 combination therapy) in
99 hospitalized COVID-19 patients were also terminated for futility with sample sizes of 344

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100 and 343 respectively.²⁵ On first principles, the clinical response to antibody-based
101 therapies may be greatest in individuals early in disease or who fail to mount an effective
102 immune response. This is supported by evidence of clinical benefit in early disease and
103 evidence that baseline anti-SARS-CoV-2 antibody status may be an important predictor
104 of the effect of anti-spike mAbs on viral load.^{15,16,19} A significant proportion of hospitalised
105 COVID-19 patients are seronegative on admission, and although a greater proportion
106 already have detectable anti-SARS-CoV-2 antibodies, the quality of their immunological
107 response may be poor since it has failed to prevent disease progression.²⁶ As such, anti-
108 spike mAbs may have benefit even in later COVID-19 disease. Here we report the results
109 of a large randomised controlled trial of REGEN-COV in patients hospitalised with
110 COVID-19.

111

112 **METHODS**

113 **Study design and participants**

114 The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is an investigator-
115 initiated, individually randomised, controlled, open-label, platform trial to evaluate the
116 effects of potential treatments in patients hospitalised with COVID-19. Details of the trial
117 design and results for other possible treatments (dexamethasone, hydroxychloroquine,
118 lopinavir-ritonavir, azithromycin, tocilizumab, convalescent plasma, colchicine and
119 aspirin) have been published previously.^{20,21,26-30} The trial is underway at 177 hospitals in
120 the United Kingdom supported by the National Institute for Health Research Clinical
121 Research Network, two hospitals in Indonesia, and two hospitals in Nepal (appendix pp

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122 3-27). Of these, 127 UK hospitals took part in the evaluation of REGEN-COV. The trial is
123 coordinated by the Nuffield Department of Population Health at the University of Oxford
124 (Oxford, UK), the trial sponsor. The trial is conducted in accordance with the principles of
125 the International Conference on Harmonisation–Good Clinical Practice guidelines and
126 approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and
127 the Cambridge East Research Ethics Committee (ref: 20/EE/0101). The protocol and
128 statistical analysis plan are available in the appendix (pp 68-148) with additional
129 information available on the study website www.recoverytrial.net.

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

138 **Randomisation and masking**

139 Baseline data were collected using a web-based case report form that included
140 demographics, level of respiratory support, major comorbidities, suitability of the study
141 treatment for a particular patient, and treatment availability at the study site (appendix pp
142 34-36).

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143 Baseline presence of anti-SARS-CoV-2 antibodies was to be determined for each
144 participant using serum samples taken at the time of randomisation. Analysis was done
145 at a central laboratory with a validated 384 well plate indirect ELISA for anti-spike IgG
146 (appendix p 28).³¹ Participants were categorised as seropositive or seronegative using a
147 predefined assay threshold with a 99% or higher sensitivity and specificity in detecting
148 individuals with SARS-CoV-2 infection at least 20 days previously.³¹

149 Eligible and consenting patients were assigned in a 1:1:1 ratio to either usual standard of
150 care, usual standard of care plus REGEN-COV or usual standard of care plus
151 convalescent plasma (until 15 January 2021), using web-based simple (unstratified)
152 randomisation with allocation concealed until after randomisation (appendix pp 32-33).
153 For some patients, REGEN-COV was unavailable at the hospital at the time of enrolment
154 or was considered by the managing physician to be either definitely indicated or definitely
155 contraindicated. These patients were excluded from the randomised comparison between
156 REGEN-COV and usual care. Patients allocated to REGEN-COV were to receive a single
157 dose of REGEN-COV 8g (casirivimab 4g and imdevimab 4g) in 250ml 0.9% saline infused
158 intravenously over 60 minutes +/- 15 minutes as soon as possible after randomisation.

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

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

168 **Procedures**

169 Early safety outcomes were recorded by site staff using an online form 72 hours after
170 randomisation (appendix pp 37–41). An online follow-up form was completed by site staff
171 when patients were discharged, had died, or at 28 days after randomisation, whichever
172 occurred first (appendix pp 42–48). Information was recorded on adherence to allocated
173 trial treatment, receipt of other COVID-19 treatments, duration of admission, receipt of
174 respiratory or renal support, and vital status (including cause of death). In addition, routine
175 health-care and registry data were obtained, including information on vital status at day
176 28 (with date and cause of death); discharge from hospital; and receipt of respiratory
177 support or renal replacement therapy.

178 **Outcomes**

179 Outcomes were assessed at 28 days after randomisation, with further analyses specified
180 at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes
181 were time to discharge from hospital, and, among patients not on invasive mechanical
182 ventilation at randomisation, the composite outcome of invasive mechanical ventilation
183 (including extra-corporeal membrane oxygenation) or death. Prespecified subsidiary
184 clinical outcomes were use of invasive or non-invasive ventilation among patients not on
185 any ventilation at randomisation, time to successful cessation of invasive mechanical
186 ventilation (defined as cessation of invasive mechanical ventilation within, and survival to,
187 28 days), and use of renal dialysis or haemofiltration. Information on suspected serious

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

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

197 **Statistical Analysis**

198 For all outcomes, intention-to-treat analyses compared patients randomised to REGEN-
199 COV with patients randomised to usual care but for whom REGEN-COV was both
200 available and suitable as a treatment. For the primary outcome of 28-day mortality, the
201 log-rank observed minus expected statistic and its variance were used to both test the
202 null hypothesis of equal survival curves (i.e., the log-rank test) and to calculate the one-
203 step estimate of the average mortality rate ratio. We constructed Kaplan-Meier survival
204 curves to display cumulative mortality over the 28-day period.

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

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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,

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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

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

258

259 **RESULTS**

260 Between 18 September 2020 and 22 May 2021, 11464 (47%) of 24343 patients enrolled
261 into the RECOVERY trial at one of the 127 sites were eligible to be randomly allocated to
262 REGEN-COV (i.e. REGEN-COV was available in the hospital at the time and the
263 attending clinician was of the opinion that the patient had no known indication for or
264 contraindication to REGEN-COV, figure 1). 4839 patients were randomly allocated to
265 REGEN-COV and 4946 were randomly allocated to usual care. The mean age of study
266 participants in this comparison was 61.9 years (SD 14.5) and the median time since
267 symptom onset was 9 days (IQR 6 to 12 days) (webtable 1). At randomisation, 9169
268 (94%) patients were receiving corticosteroids. 5272 (54%) were seropositive at baseline,
269 3153 (32%) were seronegative, and serostatus was unknown for 1360 (14%) (table 1,
270 webtables 1 and 2).

271 The follow-up form was completed for 4773 (99%) in the REGEN-COV group and 4899
272 (99%) in the usual care group. Among patients with a completed follow-up form, 90%
273 allocated to REGEN-COV received the treatment compared with <1% allocated to usual
274 care (figure 1). Use of other treatments for COVID-19 was similar among patients
275 allocated REGEN-COV and among those allocated usual care, with about one-quarter

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

278 Among patients who were known to be seronegative at baseline, allocation to REGEN-
279 COV was associated with a significant reduction in the primary outcome of 28-day
280 mortality compared with usual care alone: 396 (24%) of 1633 patients in the REGEN-
281 COV group died vs 451 (30%) of 1520 patients in the usual care group (rate ratio 0.80;
282 95% CI, 0.70–0.91; $p=0.0010$; table 2, figure 2a, and figure 3). The proportional effect of
283 REGEN-COV on mortality differed significantly between seropositive and seronegative
284 patients (test for heterogeneity $p=0.001$; figure 3). Among all patients randomised
285 (including those with negative, positive, or unknown baseline antibody status), there was
286 no significant difference in the primary outcome of 28-day mortality between the two
287 randomised groups: 944 (20%) of 4839 patients in the REGEN-COV group died vs. 1026
288 (21%) of 4946 patients in the usual care group (rate ratio 0.94; 95% CI, 0.86 to 1.03;
289 $p=0.17$; webtable 4, figure 2b, and figure 3).

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

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299 Among seronegative patients, discharge alive within 28 days was more common among
300 those allocated to REGEN-COV compared with usual care (64% vs. 58%; rate ratio 1·19,
301 95% CI 1·08 to 1·30; median 13 days [IQR 7 to >28] vs. 17 days [IQR 7 to >28]) (table 2,
302 figure 3 and webfigure 3a). However, there was no meaningful difference among the
303 overall study population (70% vs. 69%; rate ratio 1·01, 95% CI 0·97 to 1·07; median 10
304 days [IQR 6 to >28] vs. 10 days [IQR 5 to >28]) (webtable 4, figure 3 and webfigure 3b).

305 Among seronegative patients not on invasive mechanical ventilation at baseline,
306 allocation to REGEN-COV was associated with a lower risk of progressing to the
307 composite secondary outcome of invasive mechanical ventilation or death (30% vs. 37%,
308 risk ratio 0·83, 95% CI 0·75 to 0·92) (table 2 and figure 3). However, there was no
309 difference among the overall study population (24% vs. 25%, risk ratio 0·96, 95% CI 0·90
310 to 1·04) (webtable 4 and figure 3).

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

315 Among seronegative patients, allocation to REGEN-COV versus usual care was
316 associated with less frequent progression to use of ventilation among patients not on such
317 treatment at baseline versus usual care (28% vs 32%; risk ratio 0·87, 95% CI 0·77 to
318 0·98) (table 2) but not in the overall study population (23% vs. 24%; risk ratio 0·95, 95%
319 CI 0·87 to 1·04) (webtable 4). There were no meaningful differences in progression to
320 renal replacement therapy, non-COVID mortality, cardiac arrhythmia, thrombosis or major

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321 bleeding either in the seronegative or overall study populations (table 2, webtables 4, 6,
322 7 and 8).

323 Information on potential infusion reactions occurring within the first 72 hours after
324 randomisation was collected for 1792 patients in the REGEN-COV group and 1714
325 patients in the usual care group (before collection of these data stopped on 19 February
326 2021): The reported frequency of fever (4% vs. 3%), sudden hypotension (4% vs. 2%),
327 and thrombotic events (2% vs. 1%) was marginally higher in the REGEN-COV group vs.
328 the usual care group while the frequency of sudden worsening in respiratory status (21%
329 vs. 22%) and clinical haemolysis (1% vs. 2%) was marginally lower (webtable 9). There
330 were 5 reports of a serious adverse reaction believed to be related to REGEN-COV
331 (webtable 10).

332

333 **DISCUSSION**

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

337 In addition, allocation to REGEN-COV was associated with an increased rate of discharge
338 alive from hospital within the first 28 days and a reduced rate of progression to invasive
339 mechanical ventilation or death in these patients. By contrast, no such benefits were seen
340 for patients who were anti-SARS-CoV-2 antibody positive at randomisation.
341 Consequently, when all patients were considered together (including those with unknown
342 antibody status), allocation to REGEN-COV was associated with non-significant

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

349 Based on our findings, any therapeutic use of REGEN-COV in the hospital setting may
350 be best restricted to seronegative patients. This would require serological testing prior to
351 drug administration. High-performance, laboratory-based commercial assays for SARS-
352 CoV-2 antibodies are available and used in high-income healthcare settings. However,
353 they are not widely available in lower income settings.³² Point-of-care lateral-flow
354 immunoassays have been developed but some have suboptimal performance and their
355 suitability for guiding therapeutic decisions, as opposed to sero-epidemiological studies,
356 requires further evaluation.^{31,33,34} Assays with lower costs and technological requirements
357 than commercial bench-top systems and better performance than lateral-flow
358 immunoassays have been developed and may offer more scalable and affordable options
359 for serostatus evaluation but these also require further evaluation before clinical use.³⁵

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

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

367 mAbs are susceptible to the evolution of viral resistance if substitutions in the targeted
368 epitope reduce or abrogate antibody binding, and an Emergency Use Authorisation for
369 monotherapy with the mAb LY-CoV555 was revoked due to resistance in several major
370 virus variants.³⁷ This risk can be reduced by using a combination of mAbs that bind to
371 non-overlapping epitopes.¹⁴ Whilst we did not study the emergence of resistance variants
372 in this trial, the major variants circulating in the UK throughout the trial, including B.1.1.7
373 (alpha) variant which was the dominant variant in the UK from December 2020 to April
374 2021, remained sensitive to REGEN-COV.^{38,39} Although spike glycoprotein mutations in
375 some variants (e.g. B.1.351 [beta] and B.1.617 [delta]) have been associated with a
376 reduction of neutralisation activity of casirivimab, the combination of casirivimab with
377 imdevimab retains potency against these variants due to the inhibitory activity of
378 imdevimab.³⁸⁻⁴¹ However, continued monitoring of resistance patterns is imperative to
379 detect variants with resistance to both components.

380 Strengths of this trial included that it was randomised, had a large sample size, broad
381 eligibility criteria and more than 99% of patients were followed up for the primary outcome.
382 Information on virological outcomes was not collected, nor was information on radiological
383 or physiological outcomes. Although this randomised trial is open label (i.e., participants
384 and local hospital staff are aware of the assigned treatment), the outcomes are
385 unambiguous and were ascertained without bias through linkage to routine health
386 records. The dose of REGEN-COV used in this study was high compared to those used

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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

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393 **Contributors**

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

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413 * PWH and MM made an equal contribution

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415 **Data Monitoring Committee**

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420 **Declaration of interests**

421 DMW is an employee of Regeneron Pharmaceuticals and holds shares/share options in
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426 at the University of Oxford has a staff policy of not accepting honoraria or consultancy
427 fees directly or indirectly from industry (see [https://www.ndph.ox.ac.uk/files/about/ndph-](https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf)
428 [independence-of-research-policy-jun-20.pdf](https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf)).

429 **Data sharing**

430 The protocol, consent form, statistical analysis plan, definition & derivation of clinical
431 characteristics & outcomes, training materials, regulatory documents, and other relevant
432 study materials are available online at www.recoverytrial.net. As described in the protocol,
433 the trial Steering Committee will facilitate the use of the study data and approval will not
434 be unreasonably withheld. Deidentified participant data will be made available to bona
435 fide researchers registered with an appropriate institution within 3 months of publication.
436 However, the Steering Committee will need to be satisfied that any proposed publication
437 is of high quality, honours the commitments made to the study participants in the consent
438 documentation and ethical approvals, and is compliant with relevant legal and regulatory
439 requirements (e.g. relating to data protection and privacy). The Steering Committee will
440 have the right to review and comment on any draft manuscripts prior to publication. Data
441 will be made available in line with the policy and procedures described at:
442 <https://www.ndph.ox.ac.uk/data-access>. Those wishing to request access should
443 complete the form at
444 https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx
445 and e-mailed to: data.access@ndph.ox.ac.uk

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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

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Figure 1: Trial profile – Flow of participants through the RECOVERY trial
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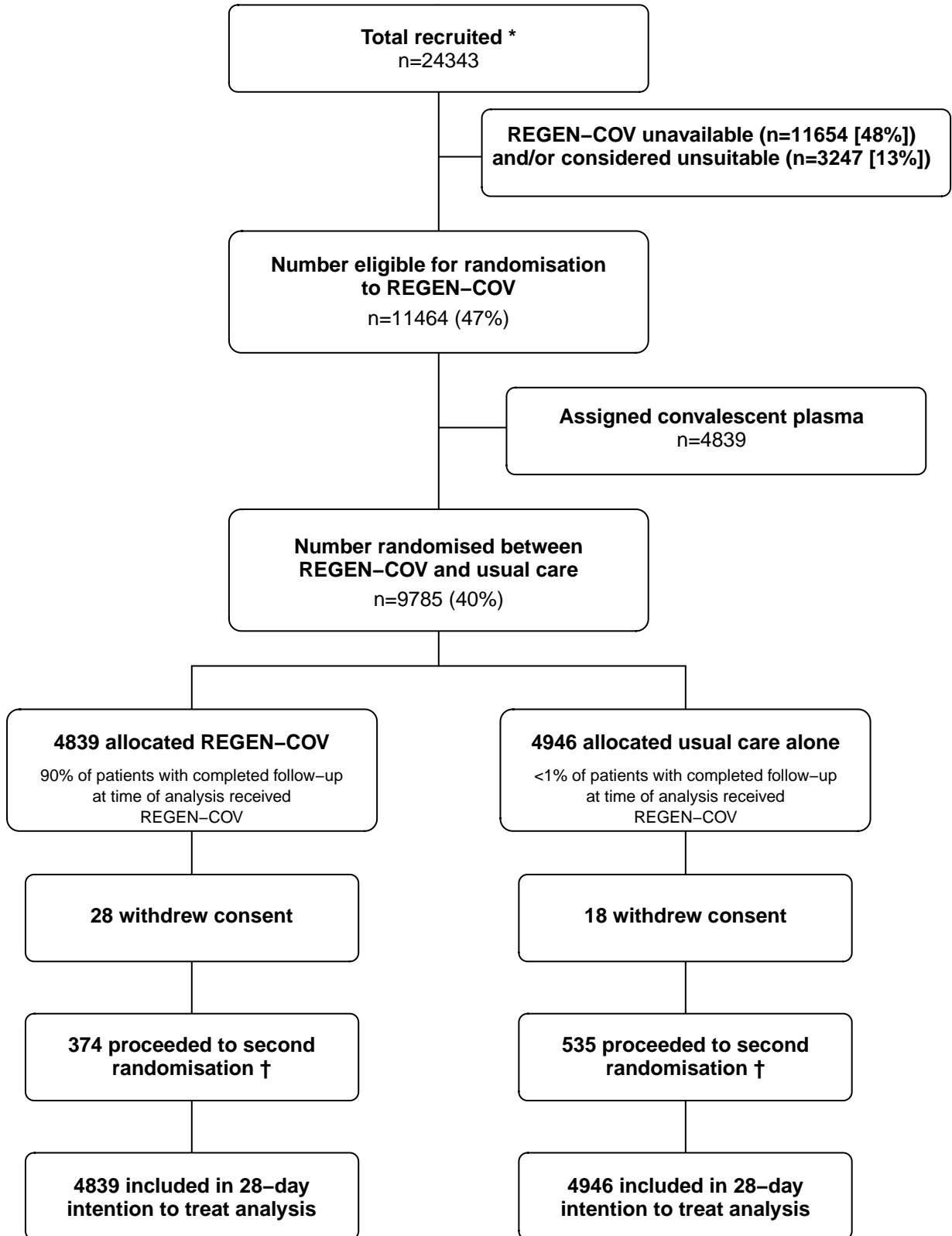
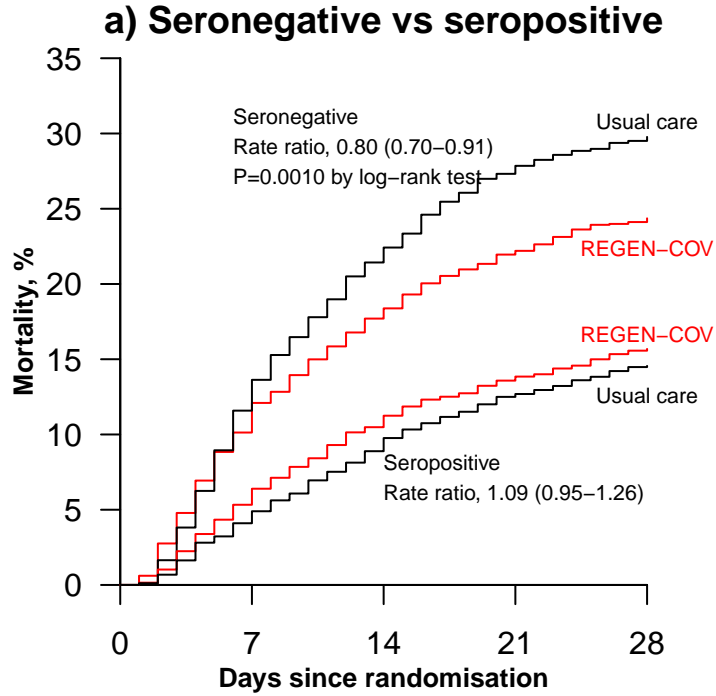


Figure 2: Effect of allocation to REGEN-COV on 28-day mortality in: a) seronegative vs seropositive participants; and b) all participants

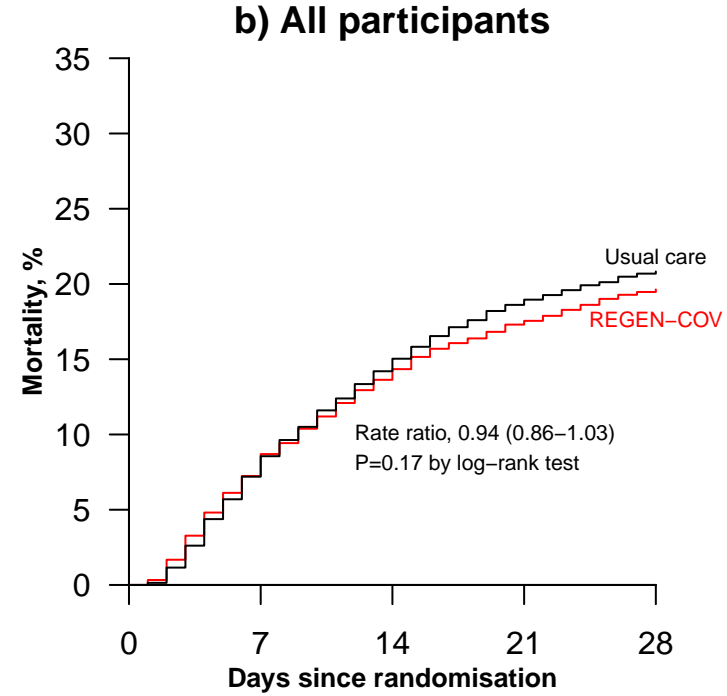


No. at risk, Seronegative

REGEN-COV	1633	1429	1325	1260	1224
Usual Care	1520	1308	1173	1088	1059

No. at risk, Seropositive

REGEN-COV	2636	2452	2322	2252	2201
Usual Care	2636	2503	2375	2292	2243



No. at risk

REGEN-COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3888

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

