

Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST)

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1 **Namilumab or infliximab compared to standard of care in hospitalised patients with COVID-19**
2 **(CATALYST): a phase 2 randomised multicentre open adaptive multi-arm multi-stage trial**

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50 **Summary**

51 **Background**

52 Dysregulated inflammation is associated with poor outcomes in Coronavirus disease 2019 (COVID-19).
53 We assessed the efficacy of namilumab, a granulocyte-macrophage colony-stimulating factor inhibitor
54 and infliximab, a tumour necrosis factor inhibitor in hospitalised patients with COVID-19 in order to
55 prioritise agents for phase 3 trials.

56 **Methods**

57 In this randomised, multi-arm, parallel group, open label, adaptive phase 2 proof-of-concept trial
58 (CATALYST) we recruited hospitalised patients ≥ 16 years with COVID-19 pneumonia and C-reactive
59 protein (CRP) ≥ 40 mg/L in nine UK hospitals. Participants were randomly allocated with equal
60 probability to usual care, or usual care plus a single 150mg intravenous dose of namilumab (150mg)
61 or infliximab (5mg/kg). Randomisation was stratified for ward versus ICU. The primary endpoint was
62 improvement in inflammation in intervention arms compared to control as measured by CRP over
63 time, analysed using Bayesian multi-level models. ISRCTN registry number 40580903.

64 **Findings**

65 Between 15th June 2020 and 18th February 2021 we randomised 146 participants: 54 to usual care, 57
66 to namilumab and 35 to infliximab. The probabilities that namilumab and infliximab were superior to
67 usual care in reducing CRP over time were 97% and 15% with point estimates for treatment-time
68 interactions of -0.09 (-0.19, 0.00) and 0.06 (-0.05, 0.17) respectively. Consistent effects were seen in
69 ward and ICU patients and aligned with clinical outcomes, such that the probability of discharge (WHO
70 levels 1-3) at day 28 was 47% and 64% for ICU and ward patients on usual care, versus 66% and 77%
71 for patients treated with namilumab. Death occurred in 6 (11%) and 10 (19%) namilumab and usual
72 care patients respectively, and 4 (14%) and 5 (15%) infliximab and usual care patients respectively.
73 134 adverse events occurred in 30/55 (55%) namilumab patients compared to 145 in 29/54 (54%)
74 usual care patients. 102 events occurred in 20/29 (69%) infliximab patients versus 112 events in 17/34
75 (50%) usual care patients.

76 **Interpretation**

77 Namilumab, but not infliximab, demonstrated proof-of-concept evidence for reduction in
78 inflammation in hospitalised patients with COVID-19 pneumonia which was consistent with secondary
79 clinical outcomes. Namilumab should be prioritised for further investigation in COVID-19.

80 **Funding**

82 **Introduction**

83 Severe Coronavirus disease 2019 (COVID-19) is associated with high mortality and disability in
84 survivors. An excessive and dysregulated immune response contributes to these poor outcomes, as
85 evidenced by the ability of corticosteroids and IL-6 receptor blockade to reduce mortality in
86 hospitalised patients requiring oxygen.^{1,2}

87 Inflammatory monocytes/macrophages (IMM) appear central to this dysregulated response,³
88 resulting in disruption of pulmonary endothelial barrier integrity, microvascular thrombosis,⁴ and lung
89 tissue damage.⁵ A genome-wide association study has identified the monocyte/macrophage
90 chemotactic protein CCR2 as being associated with severe COVID-19.⁶ Transcriptomic analysis of
91 blood, lung and bronchoalveolar fluid has revealed a predominance of activated IMM within the lung,
92 alongside expression of pro-coagulant genes within alveolar macrophages.⁷ Notably, the aberrant
93 expression of proliferation markers in blood monocytes correlates with severe disease,⁸ and likely
94 reflects a pathological early release of monocytes from the bone marrow.⁹ IMM may be further
95 activated and polarised to an inflammatory phenotype in severe disease by interaction with immune
96 complexes containing hypoglycosylated anti-spike protein antibodies.¹⁰

97 IMM or their activity may be targeted therapeutically in a number of different ways. Given that trials
98 with clinical outcomes require large numbers of patients to show effects, we designed a multi-arm
99 proof of concept trial with a biomarker primary outcome to expedite decision-making on potentially
100 effective therapeutic options for COVID-19. The aim was to provide early biological signals of efficacy
101 to efficiently prioritise agents with the highest likelihood of success for study in established phase 3
102 platform trials.¹¹ The first two agents studied were namilumab and infliximab.

103 Namilumab is an anti-granulocyte-macrophage colony stimulating factor (GM-CSF) monoclonal
104 antibody with a good safety profile up to phase 2 that has been studied in inflammatory conditions
105 such as rheumatoid arthritis. GM-CSF is a multifunctional cytokine that is a growth factor for
106 granulocytes and monocytes and has an important role in immune responses. In particular, it drives
107 the activation, maturation, survival and trafficking of monocyte-derived macrophages, and their
108 polarisation towards a more inflammatory phenotype. Elevated GM-CSF levels are closely associated
109 with disease severity in COVID-19,¹² with GM-CSF-expressing T cells being clonally expanded in the
110 lungs.¹³ Notably, GM-CSF may also enhance the pro-coagulant activities of macrophages,¹⁴ and blood
111 clots are a recognised side effect of recombinant GM-CSF (sargramostim), suggesting that
112 dysregulated GM-CSF expression may predispose to the microvascular thrombosis characteristic of
113 COVID-19.⁴

114 Infliximab is a widely used anti-tumour necrosis factor (TNF) monoclonal antibody. TNF is an important
115 pro-inflammatory cytokine and its inhibition has shown efficacy in many chronic immune mediated
116 inflammatory diseases (IMIDs). TNF inhibition reduces mortality and severity in several mouse models
117 of viral respiratory infection.^{15,16} An IMM subset associated with severe COVID-19 shares
118 transcriptional similarities to macrophages stimulated with both TNF and interferon gamma (IFN γ).¹⁷
119 Some data suggest that IMID patients who contract COVID-19 whilst treated with TNF inhibitors have
120 better outcomes.¹⁸

121 We sought to provide early proof-of-concept signal in a randomised trial to efficiently prioritise these
122 approaches for subsequent testing in larger trials powered for clinical outcomes. Data on harms were
123 also collected as a secondary objective.

124 **Methods**

125 **Study design**

126 The CATALYST trial is a randomised, open label, phase 2, multi-arm proof-of-concept trial.¹¹ A placebo
127 control was not included due to the operational difficulties imposed by the pandemic and the
128 proposed multi-arm design and following advice from patient and public involvement. Participants
129 were recruited from nine hospital sites in the UK (Queen Elizabeth Hospital Birmingham; Heartlands
130 Hospital, Birmingham; John Radcliffe Hospital, Oxford; Royal Bolton Hospital, Bolton; Imperial St
131 Mary's Hospital, London; Royal Hallamshire Hospital, Sheffield; University Hospital of Wales, Cardiff;
132 Good Hope Hospital, Birmingham and University College Hospital, London). The trial was approved by
133 the East Midlands-Nottingham 2 Research Ethics Committee (20/EM/0115) and given national Urgent
134 Public Health Status.

135 **Participants**

136 Eligible patients were 16 years or over, with a clinical picture strongly suggestive of SARS-CoV-2
137 pneumonia (confirmed by chest X-ray or CT scan, with or without a positive reverse transcription-
138 polymerase chain reaction (RT-PCR) assay), and with a C-Reactive Protein (CRP) ≥ 40 mg/L. The
139 requirement for raised CRP replaced an inclusion criterion for low oxygenation status (oxygen
140 saturation $\leq 94\%$ while breathing ambient air or a ratio of the partial pressure of oxygen to the fraction
141 of inspired oxygen ≤ 300 mmHg) early in the course of recruitment following a change in primary
142 outcome (see below; all protocol changes are summarised in supplementary Table 1). Exclusion
143 criteria are detailed in Supplementary Information.

144 Written informed consent was obtained from all patients with capacity. If the patient lacked capacity,
145 from severity of illness for example, informed consent was obtained from the patient's personal legal
146 representative or, if unavailable, a professional legal representative according to the requirements of
147 the UK Health Research Authority. Patients with representative consent were re-consented as soon
148 as possible after regaining capacity.

149 **Randomisation**

150 Randomisation was performed by an automated minimisation procedure that attempted to allocate
151 participants in a balanced manner between treatment arms available at the site allowing for the sole
152 stratification variable (ward or ICU) and with a 20% random component (further details in
153 Supplementary Appendix). At one site (Bolton) infliximab was unavailable as an intervention. Although
154 clinical staff were aware of treatment allocation, aggregate outcomes were not provided to them, the
155 trial management committee or the trial steering committee.

156 **Procedures**

157 Participants assigned to namilumab received a single intravenous (IV) dose of 150mg given over 1 hour
158 on day 1. Those receiving infliximab had a single IV dose of 5 mg/kg over 2 hours on day 1. Participants
159 were followed for 28 days. Blood tests were taken on days 1, 3, 5, 7, 9 and 14 until truncated by
160 discharge or death. Physiological measures were collected until day 14, discharge, or death, and
161 included the ratio of the oxygen saturation to fractional inspired oxygen concentration (SpO_2/FiO_2 ; SF
162 ratio). The World Health Organisation (WHO) Clinical Progression Improvement Scale was assessed
163 daily for 28 days on a 1-10 scale (online supplementary Table 2) where 1 is asymptomatic, 4 is
164 hospitalised without oxygen, 6 is hospitalised with non-invasive ventilation or high-flow nasal oxygen,
165 7 is hospitalised with mechanical ventilation and 10 is death; data for level 0 (no viral load detected)
166 was not collected.²⁰ If a patient was discharged earlier than day 28 this outcome was collected by
167 means of a diary and scheduled telephone calls.

168 **Outcomes**

169 The primary objective of the trial was to investigate whether candidate treatments could reduce
170 inflammation compared to usual care alone, in order to prioritise drugs to be evaluated in phase 3
171 trials. The primary outcome measure was CRP, collected over time until day 14. Published data
172 indicate that CRP levels and trajectory are strongly associated with clinical outcomes including
173 respiratory failure and death as well as with lung changes observed on CT.¹¹ With the objective of

174 having a rapid, biologically-driven efficacy signal using continuous, readily available data and a small
175 sample size, we had initially chosen the oxygen saturation to fraction of inspired oxygen ratio (SF ratio)
176 as the primary outcome. However, subsequent modelling of data from a large cohort of patients
177 hospitalised in the first wave, indicated that the SF ratio might not be a viable outcome measure of
178 sickness. This led to an early change in primary outcome to CRP, before any analysis of trial data, as
179 previously described.¹¹

180 Secondary outcome measures included the WHO Clinical Progression Scale as a principal clinical
181 efficacy measure as well as hospital survival status and hospital free days, all assessed up to day 28.
182 Hospital free days were defined as the number of days between date of hospital discharge to day 28,
183 with patients who died or who were alive in hospital on day 28 being incorporated as 0 hospital free
184 days. Physiological outcomes measured up to day 14 or discharge, if earlier, included the SF ratio.

185 Safety data were survival status and adverse events defined by the Common Terminology Criteria for
186 Adverse Events (CTCAE), version 4.03 which fulfilled one of the following criteria: grade ≥ 3 , secondary
187 infection or allergic reaction. Data on harms were collected until day 28, utilising telephone follow-up
188 if participant discharged earlier, and were submitted on case report forms by site investigators.
189 Attribution for SAEs was made by site investigators and reviewed by arm leads or chief investigator.
190 Given the known safety profile of infliximab, infection and allergic reaction were anticipated events.
191 Low neutrophil count was an anticipated adverse event with namilumab.

192 **Statistical analysis**

193 The data were analysed according to a pre-specified Statistical Analysis Plan. Each intervention arm
194 was compared against the control group independently, including only control patients for whom that
195 intervention was a randomisation option i.e. usual care patients randomised after the infliximab arm
196 closed or at the single site where infliximab was not a randomisation option were not included in the
197 infliximab comparison. For the primary endpoint of CRP, we used Bayesian multi-level regression
198 models²¹ that allowed for nesting of the repeated measures data within patient, and non-linear
199 responses, implemented using brms.²² Default priors as chosen by 'brms' were utilised in all models,
200 updated at any analysis point; these are chosen to be very weakly informative, the default covariance
201 structure was implemented. The full details on how these are decided upon are provided in the
202 package documentation²³.

203 Posterior probabilities for the treatment/time interaction covariates were used to conduct decision
204 making at interim analyses, specifically the probability that the covariate was < 0 indicating a positive

205 treatment effect in the direction of the intervention as per the model formulation The fitted models
206 incorporated population-level effects for both the intercept and time, random effects for the intercept
207 and time for patient, and fixed effects for age, location (ward/ICU), a main treatment effect, a
208 treatment-time interaction, a treatment-location interaction and a higher order time term.

209 For the WHO scale, we used Bayesian longitudinal ordinal regression models, implemented using
210 brms,²² including in the model formulation fixed effects for location, age, a main treatment effect and
211 a treatment-time interaction and random effects for both the intercepts and time for patient. For
212 consistency with other trials, we also calculated the time to a two-point improvement for this
213 outcome. Kaplan-Meier curves were produced for time to improvement and the Greenwood method
214 was utilised in calculating confidence intervals. Results for other outcome measures were not
215 modelled; the results are summarised graphically or tabulated. The full outline for the statistical
216 analysis of all secondary endpoints for the study is provided in the statistical analysis plan in the
217 supplementary appendix.

218

219 We present for the aforementioned models conditional probability plots, which show the mean
220 predicted values of the natural logarithm of CRP, and, for the WHO scale, the predicted probability of
221 being in each of the WHO outcome categories, conditioned on model parameter values. This enables
222 an easy to interpret visualisation of effect of treatment on these outcomes through time.

223 Where relevant we include estimates of uncertainty for any point estimates at the stated
224 confidence/probability level typically 95%.

225 Interim analyses were planned every 20 participants per arm up to 60 participants, and CRP data was
226 considered by the data monitoring committee (DMC) in the context of the emerging safety data to
227 make a recommendation as outlined in the supplementary appendix. No form of bias adjustment was
228 applied.

229 Success was defined as a 90% probability of an intervention arm being better than usual care in
230 reducing CRP as per the posterior probability for the treatment-time interaction covariate outlined
231 above, whereas less than 50% probability defined futility. The operating characteristics, based on a
232 simpler analysis of area under the curve for sequential CRP data, have been previously published,¹¹
233 and are presented in the supplementary appendix. These indicated a mean total sample size of
234 between 43 and 70 patients per comparison would be required dependent on the assumptions

235 Pre-planned subgroup analyses were conducted to ascertain the effect of treatment on the primary
236 outcome measure in participants recruited from ward and ICU, and with non-severe and severe

237 disease at baseline, with severe defined as requiring non-invasive or invasive ventilation. The effect of
238 age was also studied.¹² Post-hoc analyses were conducted to exclude participants without a positive
239 SARS-CoV2 PCR, and to assess the impact of baseline remdesivir use, smoking status and frailty.

240 The primary outcome was analysed on a modified intention to treat population, which included all
241 participants who received trial treatment and had a baseline and at least one post treatment CRP
242 measurement.

243 The modified intention to treat population for secondary outcomes included all patients who received
244 any trial treatment and with available data for the respective outcome. The safety population included
245 all patients in the usual care arm and all patients who had received a trial intervention in the active
246 arms. Data on all reported harms, as well as for those meeting the pre-specified criteria, were
247 summarised descriptively.

248 An independent data monitoring committee (DMC) reviewed unblinded data at interim analyses to
249 advise the Trial Steering Committee on whether the trial data (and results from other relevant
250 research), justified the continuing recruitment of further patients. The DMC operated in accordance
251 with a trial-specific charter based on the template created by the Damocles Group. Statistical analysis
252 was conducted in Stata 16 and R Version 4.0.3. The ISRCTN registry number is 40580903.

253 **Role of the funding source**

254 The funder of the study had no role in study design, data collection, data analysis, data interpretation,
255 or writing of the report. All authors had full access to all the data in the study and had final
256 responsibility for the decision to submit for publication.

257 **Results**

258 Between 15th June 2020 and 18th February 2021 we assessed 299 patients for eligibility and
259 randomised 146 participants to usual care (n=54), namilumab (n=57) and infliximab (n=35) (Figure 1).
260 Data from the COVID-19 genomics UK consortium (COG-UK) shows that the main circulating strains in
261 the UK within this time period were the original B lineage, the B.1.177 lineage and the B.1.1.7 lineage
262 (alpha variant). Following a DMC review on 21st January 2021 that made recommendations on both
263 arms based on primary outcome analysis, the Trial Steering Committee advised stopping the infliximab
264 arm for futility (probability of benefit 21%) but to continue to recruit to usual care and namilumab,
265 which met criteria for success (probability of benefit 99%), in order to collect further secondary
266 outcome clinical data. A subsequent DMC meeting on 23rd February 2021, advised closing the
267 remaining arms as the trial was close to maximal recruitment for these arms and recent changes to

268 standard of care with routine use of tocilizumab would affect conduct of the trial. In total 9 patients
269 withdrew post-randomisation but before treatment and were not included in the analysis: 5
270 participants at their own or a relative's request (1 namilumab and 4 infliximab), 1 patient in the usual
271 care group at the request of the treating physician, 1 patient in the infliximab group was reassessed
272 as not having COVID-19, 1 patient in the namilumab group due to initial non-disclosure of information
273 that met an exclusion criterion, and 1 patient in the infliximab group who was withdrawn before
274 treatment when the DMC recommendation to stop the arm was made known.

275 Table 1 shows the baseline characteristics for participants. Denominators are provided below to
276 indicate available data. Overall, groups were evenly matched although fewer patients in the infliximab
277 group had remdesivir at enrolment. Most participants had a positive PCR assay for SARS-CoV2. Overall,
278 53/54 (98%) patients in the usual care group, 55/57 (97%) of the namilumab group and 33/35 (94%)
279 of the infliximab group received oxygen at baseline. For the usual care and namilumab comparison,
280 16/54 (30%) and 21/57 (37%) received high-flow nasal oxygen or CPAP, and 11/54 (20%) and 11/57
281 (19%) were intubated and mechanically ventilated. Almost all patients received dexamethasone as
282 part of usual care at enrolment, and around half received remdesivir. Subsequent to enrolment, all
283 patients bar one in the namilumab group received dexamethasone, 36/53 (68%) and 37/55 (67%)
284 patients in the usual care and namilumab arms received remdesivir, and 3/53 (6%) and 5/55 (9%) in
285 the usual care and namilumab comparison received tocilizumab respectively. For the infliximab
286 comparison, all patients received dexamethasone, 26/33 (79%) and 16/30 (53%) received remdesivir
287 before or following randomisation, and 2/33 (6%) and /30 (3%) in usual care and infliximab comparison
288 received tocilizumab respectively).

289 The following patients were evaluable for the primary outcome: 45 and 52 for the usual care alone
290 versus namilumab comparison respectively, and 29 and 28 for the usual care versus infliximab
291 comparison respectively. At the whole population level, and consistent with our previous findings and
292 published data, CRP over time was related to the outcomes of discharge, death and continued
293 hospitalisation at day 28 (supplementary Figure 1). Analysis of the primary outcome showed a 97%
294 probability that namilumab plus usual care was superior to usual care alone in reducing CRP over time
295 with a point estimate for the treatment-time interaction of -0.09 (-0.19, 0.00). (Figure 2). Model fitted
296 values were in good agreement with raw data. This effect was consistent in ward and ICU groups based
297 on location at randomisation as visualised in the conditional effects plots (Figure 2), and also in 'severe'
298 and 'non-severe' patients at baseline (Supplementary Figure 2), where severe was defined as use of
299 non-invasive or invasive ventilation. The effect of namilumab on CRP was independent of age
300 (Supplementary Figure 3). The probability of infliximab being superior to usual care alone was 15%

301 with a point estimate for the treatment-time interaction of 0.06 (-0.05, 0.17). This lack of effect was
302 consistent across ward and ICU groups (Figure 2) and severe and non-severe disease (supplementary
303 Figure 2). Post-hoc sensitivity analyses were conducted to assess the impact of baseline remdesivir
304 use, smoking status and frailty, and the inference for both drugs remained unchanged (data not
305 shown). Likewise, excluding patients without a positive SARS-CoV2 PCR did not change the inference
306 (data not shown). Effects of namilumab and infliximab on CRP were also consistent with an area-
307 under-the curve analysis (data not shown). Supplementary Tables 3 and 4 show point estimates for
308 $\ln(\text{CRP})$ predicted values with associated credible intervals at baseline, day 7 and day 14 for both ward
309 and ICU patients.

310 Amongst secondary endpoints, the principal efficacy outcome was the 1-10 point WHO clinical
311 progression scale. For the modified intention-to-treat comparisons between usual care and
312 namilumab, data were available for 53 and 55 patients respectively. Figure 3 shows the proportion of
313 patients at each WHO scale level over 28 days as well as the conditional modelled probabilities of
314 being at each level over time for ward and ICU. In the namilumab arm for patients recruited from both
315 ward and ICU, the probability of having lower scores is consistently increased over time in comparison
316 with usual care. For example, the arms were similar at baseline but by day 28, the probability of
317 discharge (WHO levels 1-3 combined) was 47% and 64% for ICU and ward patients on usual care,
318 versus 66% and 77% for patients treated with namilumab (supplementary Table 5). At day 14, the
319 probability of an ICU patient still needing non-invasive ventilation, invasive ventilation or to have died
320 (WHO ≥ 6) was 54% in the usual care arm vs. 36% in the namilumab arm. Time to two point
321 improvement was also seen to be shorter in the namilumab arm (Table 2 and supplementary Figure
322 4). Comparable improvements on WHO scale were not observed with infliximab (Supplementary
323 Figure 5 and supplementary Table 6). The median hospital free days for usual care and namilumab
324 were 17 (IQR 0, 23) and 20 (IQR 3, 23) respectively, and for usual care and infliximab, 17 (0, 23) and
325 17 (3, 23). Data were also collected on respiratory rate, body temperature and destination of
326 discharge, however results were non-informative and data is not shown. Similarly, data was collected
327 on lymphocyte and neutrophil counts, neutrophil: lymphocyte ratios, and ferritin, d-dimers and lactate
328 dehydrogenase (LDH). These outcomes will be presented alongside exploratory biological outcomes
329 in a future publication.

330 By day 28, there were fewer deaths and more discharges in the namilumab group with 43 (78%)
331 participants discharged, 6 (11%) still in hospital and 6 (11%) dead, compared to 33 (62%), 11 (20%),
332 and 10 (19%) for usual care alone (Table 3). Interestingly, despite the challenges we described in

333 modelling the SF ratio, trends to improvement in oxygenation status were observed with namilumab
334 (supplementary Figure 6).

335 For the namilumab and usual care comparison, a total of 279 adverse events were reported in 59 of
336 the 109 patients in the safety population (54%; 134 events in n=30 and 145 events in n=29 for
337 namilumab and usual care respectively). Of these, 131 (90%) and 103 events (77%) events were grade
338 3 or above for usual care and namilumab respectively. Infections were more common in the
339 namilumab group (20 events) compared with usual care (10 events). Supplementary Table 7 shows
340 adverse events that were grade ≥ 3 , secondary infection or allergic reaction, for which more than one
341 event occurred. There were 10 serious adverse events in each of the usual care and namilumab groups
342 respectively. All except one of the namilumab SAEs were considered unrelated, the related case being
343 a re-admission with bacterial pneumonia 26 days after receiving namilumab and on a background of
344 a prolonged admission for social reasons and known COPD.

345 For the infliximab and usual care comparison, a total of 214 adverse events were reported in 37 of the
346 63 patients in the safety population (60%; 112 events in 17 usual care patients and 102 events in 20
347 infliximab patients). Of these, 101 (90%) and 78 (77%) were grade 3 or above for usual care and
348 infliximab respectively. There were 7 infection events in usual care and 4 with infliximab. There were
349 5 serious adverse events in the usual care group and 6 with infliximab, all considered unrelated. There
350 were no deaths in the safety population outside of the MITT population.

351

352 **Discussion**

353 Our trial clearly demonstrated that the addition of namilumab, but not infliximab to usual care,
354 reduced inflammation as measured by CRP in hospitalised patients with COVID-19, when compared
355 to usual care alone. Importantly, the secondary clinical outcomes are consistent and shared the same
356 directionality as the primary outcome for both interventions, despite not being formally powered to
357 assess for such differences. Our proof-of-concept findings with GM-CSF inhibition is consistent with
358 our hypothesis that recruitment and activation of IMM are important in the pathogenesis of severe
359 COVID-19. This is also consistent with published findings from small non-randomised trials,^{24,25} and
360 recent, large randomised trials of other GM-CSF inhibitors in COVID-19. Otilimab showed benefit for
361 the primary endpoint of being alive and free of respiratory failure at day 28 in a predefined subgroup
362 of patients aged 70 or over.²⁶ Lenzilumab, given as a three dose course in non-ventilated hospitalised
363 patients, showed benefit over standard care in the primary outcome of survival without ventilation,

364 an effect that seemed more pronounced in patients aged 85 or under and with CRP <150 mg/L.²⁷ Our
365 data suggest the effect of a single dose of namilumab on CRP and WHO score is independent of age,
366 although this requires confirmation in larger studies. Although it is not possible to directly compare
367 these studies given the differences in sample sizes, inclusion criteria and study designs, the overall
368 RCT data suggest benefit of GM-CSF inhibition in COVID-19. For, example, we observed mortality in
369 the namilumab group of 11% compared to 19% with usual care. In the lenzilumab and otilimab phase
370 3 trials this was 10% in the active arm compared to 14% (day 28), and 23% versus 24% (day 60)
371 respectively. In two recent phase 2 mavrilimumab trials, mortality was 8% versus 21%²⁸, and 5%
372 compared to 16%²⁹. Benefit has also been observed with IL-6 inhibition with a recent meta-analysis
373 showing a day 28 mortality of 22% in the active arms compared to 25% with usual care/placebo³⁰.

374 In the absence of large treatment effects, small trials using traditional clinical outcomes may give
375 inconclusive or contrary findings in COVID-19, as exemplified by earlier studies of tocilizumab. The
376 CATALYST trial was designed to use a repeatedly collected continuous measure of CRP with a Bayesian
377 adaptive approach that we predicted would require a smaller sample size to show evidence of efficacy
378 or futility. CRP levels, including the rate of decline, have been associated with clinical outcome in
379 COVID-19 (reviewed in¹¹) and we hypothesised that an immunomodulatory agent unable to alter CRP
380 would be a less promising candidate to take forward into phase 3 trials. In the face of many options
381 for repurposing immunomodulatory therapies in COVID-19, we contend that such a prioritisation
382 approach will make the most efficient use of phase 3 resource and accelerate development of effective
383 drugs.

384 In contrast to the observed effect of namilumab, we could not demonstrate a comparable benefit on
385 CRP with infliximab and the arm was stopped for futility. TNF is an important pro-inflammatory
386 cytokine produced by macrophages as well as other cell types, with context-dependent pleiotropic
387 effects including further activation of IMM and up-regulation of inflammatory mediators such as IL-6.
388 One previous non-randomised study of infliximab suggested potential efficacy, albeit with significant
389 limitations including small sample size, use of historical controls, and being conducted prior to routine
390 use of corticosteroids.³¹ This, together with circumstantial data, justified our inclusion of infliximab.¹⁸
391 However, although TNF inhibitors are widely used in inflammatory diseases, not all IMID are
392 responsive, and TNF itself may suppress certain pro-inflammatory factors that may be relevant to
393 COVID-19 such as type 1 interferon expression and Th17 cell differentiation.³² Inhibition of such cross-
394 regulatory effects may underlie our negative findings, or simply indicate that TNF is not on a critical
395 path to driving inflammatory responses as measured by CRP in patients hospitalised with COVID-19.
396 GM-CSF inhibition might also have an additional benefit in retarding neutrophil recruitment and
397 activation that may be of importance in the pathogenesis of severe COVID-19 and acute respiratory

398 distress syndrome.³³ Our safety data suggest that the lack of response to infliximab is not due to an
399 increase in secondary infections. We cannot exclude the possibility of benefit with infliximab being
400 seen in a subset of patients, in larger studies, or with a dose higher than the standard dose we
401 employed although this was in large molar excess relative to published concentrations of circulating
402 TNF in COVID-19. It should also be noted that remdesivir use was lower in the infliximab arm when
403 compared to usual care, although the recent negative SOLIDARITY trial for remdesivir suggest this
404 might not unduly influence our results ³⁴, and results of our post-hoc sensitivity analyses were
405 consistent. However, the clear divergence in primary outcome is broadly reflected in the secondary
406 clinical findings and justifies the prioritisation of GM-CSF inhibition over TNF inhibition at this dose for
407 further study in hospitalised COVID-19 patients.

408 GM-CSF has an important role in the differentiation of alveolar macrophages, and consequently in
409 surfactant clearance, as well as being an important survival factor for lung epithelial cells. Absence of
410 GM-CSF signalling, through genetic defect in the receptor or very high levels of polyclonal
411 autoantibodies to GM-CSF, have been associated with pulmonary alveolar proteinosis (PAP). PAP has
412 been an adverse event of special interest in previous clinical trials of GM-CSF inhibitors but, to our
413 knowledge, has never been observed. It is important to note, (i) that therapeutic monoclonal
414 antibodies will not completely inhibit GM-CSF signalling which appears to be a requirement for PAP,³⁵
415 but rather will down-regulate excessive pathway activation, (ii) lack of GM-CSF does not prevent
416 macrophage uptake of surfactant as much as its catabolism, therefore the effect of short-term
417 inhibition is likely to be less pronounced on surfactant clearance when compared with long-term
418 inhibition, (iii) down regulation of monocyte activation, which is the aim of GM-CSF inhibition, should
419 itself lead to a reduction in alveolar epithelial cell damage in COVID-19. However it is also important
420 to note an opposing view that administration of GM-CSF might have therapeutic benefits and the
421 results of clinical trials of inhaled and intravenous sargramostim are awaited.³⁶

422 Our study has a number of limitations. Similar to many other trials in COVID-19 we did not use a
423 placebo control. However, the discordant results of the two active arms, when compared to usual
424 care, as well as the objective nature of CRP data, suggest this does not explain the positive findings
425 we observed with namilumab. Our sample size is too small for a definitive assessment of clinical
426 outcomes and further studies are required for this as well as to understand better the population that
427 may benefit most. Our results may not generalise to hospitalised patients without evidence of
428 pneumonia or raised CRP or patients not requiring hospitalisation. Harms data are difficult to interpret
429 given the small number of participants, lack of blinding, the severity of the background illness and that
430 data was being collected during a pandemic. Overall the number of total adverse events did not differ
431 between namilumab and usual care. However, our data do emphasise the need to monitor secondary

432 infections in future COVID-19 trials, particularly given the use of combination immune-modulating
433 treatments.

434 Despite the advances of dexamethasone and tocilizumab in COVID-19, mortality amongst patients
435 with severe disease remain high.² There therefore remains considerable unmet medical need, and
436 data pointing to the role of both IMM and GM-CSF in severe COVID-19, together with our findings
437 reported here, strongly suggest that targeted GM-CSF inhibitors such as namilumab should be further
438 investigated in hospitalised patients with COVID-19.

439

440 **Research in Context**

441 **Evidence before this study**

442 We searched Pubmed and medRxiv on 10th May 2021, using the following search terms [(randomised
443 OR trial) AND (anti-GM-CSF OR namilumab OR mavrilimumab OR otilimab OR lenzilumab OR
444 gimsilumab OR TJ003234 OR anti-TNF OR infliximab OR adalimumab OR etanercept OR golimumab OR
445 certolizumab) AND (COVID* OR SARS-CoV-2 OR SARS-CoV)]. Two small non-randomised studies with
446 drugs targeting GM-CSF or its receptor (lenzilumab and mavrilimumab) and one study with a TNF
447 inhibitor (infliximab) have all suggested potential efficacy but with significant limitations of small
448 sample size, use of historical controls, and being conducted prior to routine use of corticosteroids.
449 One RCT with mavrilimumab was small and inconclusive. Two larger RCTs with other anti-GM-CSF
450 inhibitors have recently been published. Otilimab showed benefit for the primary endpoint of being
451 alive and free of respiratory failure at day 28 in a predefined subgroup of patients aged 70 or over.
452 Lenzilumab, given as a three dose course, in non-ventilated hospitalised patients showed benefit over
453 standard care in the primary outcome of survival without ventilation, an effect that seemed more
454 pronounced in patients aged 85 or under and with CRP <150 mg/L. We identified no published
455 randomised trials of TNF inhibitors in COVID-19.

456 **Added value of this study**

457 This is the first randomised trial of namilumab and infliximab in COVID-19. We found that both drugs
458 were safe and that namilumab, but not infliximab, showed proof of concept evidence of reduction in
459 inflammation as measured by CRP in hospitalised patients with COVID-19 pneumonia. Secondary
460 clinical outcomes were concordant with the primary outcome, with trends to improvement in patients
461 recruited from both ward and ICU.

462 **Implications of all the available evidence**

463 Consistent with emerging evidence implicating GM-CSF and inflammatory monocytes/macrophages
464 in the pathogenesis of severe COVID-19, namilumab improved both biological and clinical outcomes.
465 It should be prioritised for further study in COVID-19.

466 **Contributors**

467 BAF, TV, MR, TW, DP, AR, RS, DRT, JB, SG, DR and PK conceived the study. BAF, TV, DS, MR, TW, DP,
468 AR, RS, DRT, JB, HM, LH, PNN, SG, DR and PK designed the clinical trial. BAF and DP were arm leads
469 for namilumab and MR and DR were arm leads for infliximab. TV, TW, JS, DP, MSB, GC, NM, ZG,
470 MPW, JP and AR recruited patients and/or collected data. DS, CG and SG conducted the statistical
471 analysis and had access to the raw data and verified the data. BAF drafted the manuscript which all
472 authors revised and approved for submission.

473 **Declaration of interests**

474 BAF has undertaken consultancy for Novartis, BMS, Servier, Galapagos and Janssen and received
475 research funding from Servier and Galapagos; MR is currently undertaking a Senior Clinical Fellowship
476 financed by Roche; PK has undertaken consultancy for BMS, and AstraZeneca, and has received
477 research funding from Bayer and Pfizer; DR is a former employee of GSK; all are unrelated to this trial.
478 All other authors declare no competing interests.

479 **Data sharing**

480 Participant data and the associated supporting documentation will be available within six months after
481 the publication of this manuscript. Details of our data request process are available on the Cancer
482 Research UK Clinical Trials Unit (CRCTU) website. Only scientifically sound proposals from
483 appropriately qualified research groups will be considered for data sharing. The decision to release
484 data will be made by the CRCTU Director's Committee, who will consider the scientific validity of the
485 request, the qualifications and resources of the research group, the views of the Chief Investigator
486 and the Trial Steering Committee, consent arrangements, the practicality of anonymising the
487 requested data and contractual obligations. A data sharing agreement will cover the terms and
488 conditions of the release of trial data and will include publication requirements, authorship and
489 acknowledgements and obligations for the responsible use of data. An anonymised encrypted dataset

490 will be transferred directly using a secure method and in accordance with the University of
491 Birmingham's IT guidance on encryption of datasets.

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504

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- 592
- 593

594 **Table 1.** Baseline characteristics of all patients randomised.

		Namilumab		Infliximab	
		Usual care alone (n=54)	Active arm (n=57)	Usual care alone (n=34)	Active arm (n=35)
Male n(%)		37 (69)	34 (60)	21 (62)	19 (54)
Age, median (IQR)		62.8 (51.9, 70.5)	56.2 (47.6, 63.3)	64.5 (51.9, 71.9)	55.4 (46.1, 70.5)
Ethnicity	White, n (%)	33 (61)	34 (60)	23 (68)	17 (49)
	Black	1 (2)	1 (2)	0 (0)	2 (6)
	South Asian	7 (13)	8 (14)	3 (9)	4 (11)
	Other	11 (20)	14 (25)	7 (21)	9 (26)
	Not known	2 (4)	0 (0.0)	1 (3)	3 (9)
Clinical Frailty score, level 4-8¹, n (%)		7 (13)	4 (7)	5 (15)	5 (14)
Smoking status	Ever, n (%)	22 (41)	15 (26)	11 (32)	12 (34)
Body mass index, median (IQR)		29.5 (25.4, 34.7)	30.5 (27.1, 35.4)	30.7 (25.2, 34.3)	32.3 (26.9, 35.9)
Background respiratory disease³, n(%)		13 (24)	13 (23)	10 (29)	8 (23)
Background diabetes, n(%)		22 (41)	17 (30)	12 (35)	11 (31)
Care status	Ward	33 (61)	33 (58)	22 (65)	22 (63)
	ICU	21 (39)	24 (42)	12 (35)	13 (37)
SARS-CoV2 PCR result n(%)	Positive	50 (93)	54 (95)	30 (88)	29 (83)
	Negative	3 (6)	2 (4)	3 (9)	6 (17)
Previous COVID-19 treatment at baseline, n (%)	Corticosteroids	49 (91)	53 (93)	29 (85)	33 (94)
	Remdesivir	29 (54)	32 (56)	21 (62)	10 (29)
	Antibiotics	46 (85)	48 (84)	28 (82)	31 (89)
Time to enrolment (days), median (IQR)		1 (1,3)	1 (1,2)	2 (1, 3)	1 (1, 2)
CRP, median (IQR)		108.0 (60.0, 160.0)	94.6 (55.4, 171.0)	88.0 (48.8, 142.0)	99.0 (46.0, 173.0)
Lymphocyte count, median (IQR)		0.8 (0.6, 1.2)	0.9 (0.6, 1.1)	0.9 (0.6, 1.3)	0.9 (0.6, 1.0)
Neutrophil count, median (IQR)		7.2 (5.4, 10.0)	7.5 (5.0, 10.1)	7.2 (5.5, 11.0)	6.8 (4.5, 9.5)
Ferritin, median (IQR), n=51, 37		750 (490, 1685)	791 (433, 1621)	676 (506, 1022)	642 (435, 1114)
D-dimers, median (IQR), n=57, 47		787 (376, 1822)	592 (227, 1418)	739 (414, 1184)	398 (235, 805)

595 ¹Vulnerable, mildly frail, moderately frail, severely frail. ²Time from date of hospital admission to date of randomisation.596 ³The number of patients that have at least one of the following lung disease co-morbidities (chronic obstructive pulmonary disease, asthma, interstitial lung disease).

597

598

599 **Table 2** – Median time in days (95% CI) to a two point improvement in the WHO clinical progression
 600 scale, for overall and subgroups for both drugs (modified intention to treat population). NR, not
 601 recordable.

	Namilumab			Infliximab		
	n	Usual care	Active arm	n	Usual care	Active arm
Whole population	108	10 (7,12)	8 (6,9)	62	10 (6, 14)	15 (6, 21)
Ward	66	9 (6,12)	8 (5,10)	42	9 (5, 12)	15 (5, NR)
ICU	42	14 (5,NR)	8 (6,11)	20	14 (4, NR)	19 (6, 28)

602 NR, not recordable.

603

604

605

606 **Table 3.** Hospital discharge status at day 28. Data was available on all patients (modified intention to
 607 treat population), n(%). Difference in proportions (95% CI).

	Status	Namilumab			Infliximab		
		Usual care (n=54)	Active arm (n=55)	Usual Care vs Namilumab	Usual care (n=34)	Active arm (n=29)	Usual Care vs Infliximab
Whole population	Discharge	33 (61)	43 (78)	-0.17 (-0.34, - 0.001)	22 (65)	22 (76)	-0.11 (-0.34, 0.11)
	In hospital	11 (20)	6 (11)	0.09 (-0.04, 0.23)	7 (21)	3 (10)	0.10 (-0.07, 0.28)
	Death	10 (19)	6 (11)	0.08 (-0.06, 0.21)	5 (15)	4 (14)	0.01 (-0.16, 0.18)
Ward	Discharge	28 (85)	29 (88)	-0.03 (-0.20, 0.14)	19 (86)	16 (80)	0.06 (-0.16, 0.29)
	In hospital	4 (12)	2 (6)	0.06 (-0.08, 0.20)	2 (9)	1 (5)	0.04 (-0.11, 0.19)
	Death	1 (3)	2 (6)	-0.03 (-0.13, 0.07)	1 (5)	3 (15)	-0.10 (-0.28, 0.07)
ICU	Discharge	5 (24)	14 (64)	-0.40 (-0.67, - 0.13)	3 (25)	6 (67)	-0.42 (-0.81, - 0.02)
	In hospital	7 (33)	4 (18)	0.15 (-0.11, 0.41)	5 (42)	2 (22)	0.19 (-0.19, 0.58)
	Death	9 (43)	4 (18)	0.25 (-0.02, 0.51)	4 (33)	1 (11)	0.22 (-0.11, 0.56)

608

609

611 **Figure Legends**

612 **Figure 1.** Trial profile indicating number of subjects evaluable for the primary outcome.

613 **Figure 2.** Conditional effects plots of the natural logarithm of CRP modelled over time in days in
614 patients recruited in ward and ICU for namilumab (A) and infliximab (B).

615 **Figure 3.** WHO clinical progression score over 28 days for usual care versus namilumab. A, stacked
616 bar chart of raw data for whole population eligible for comparison. B, conditional effects plots of
617 WHO score modelled over time in days showing the probability of being at each level on each day
618 for patients recruited in ICU and ward.

619

620

621

622

Figure 1.

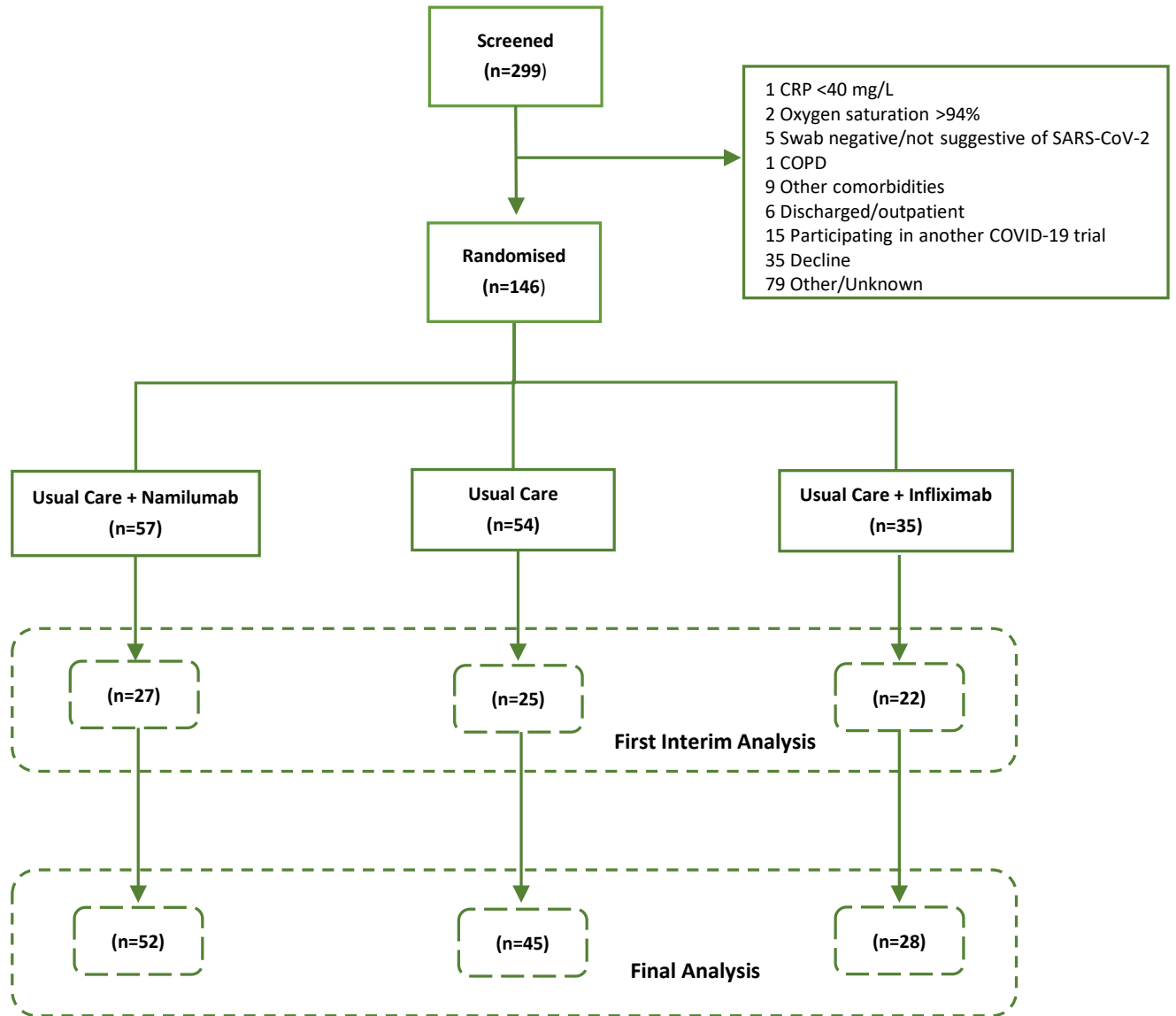
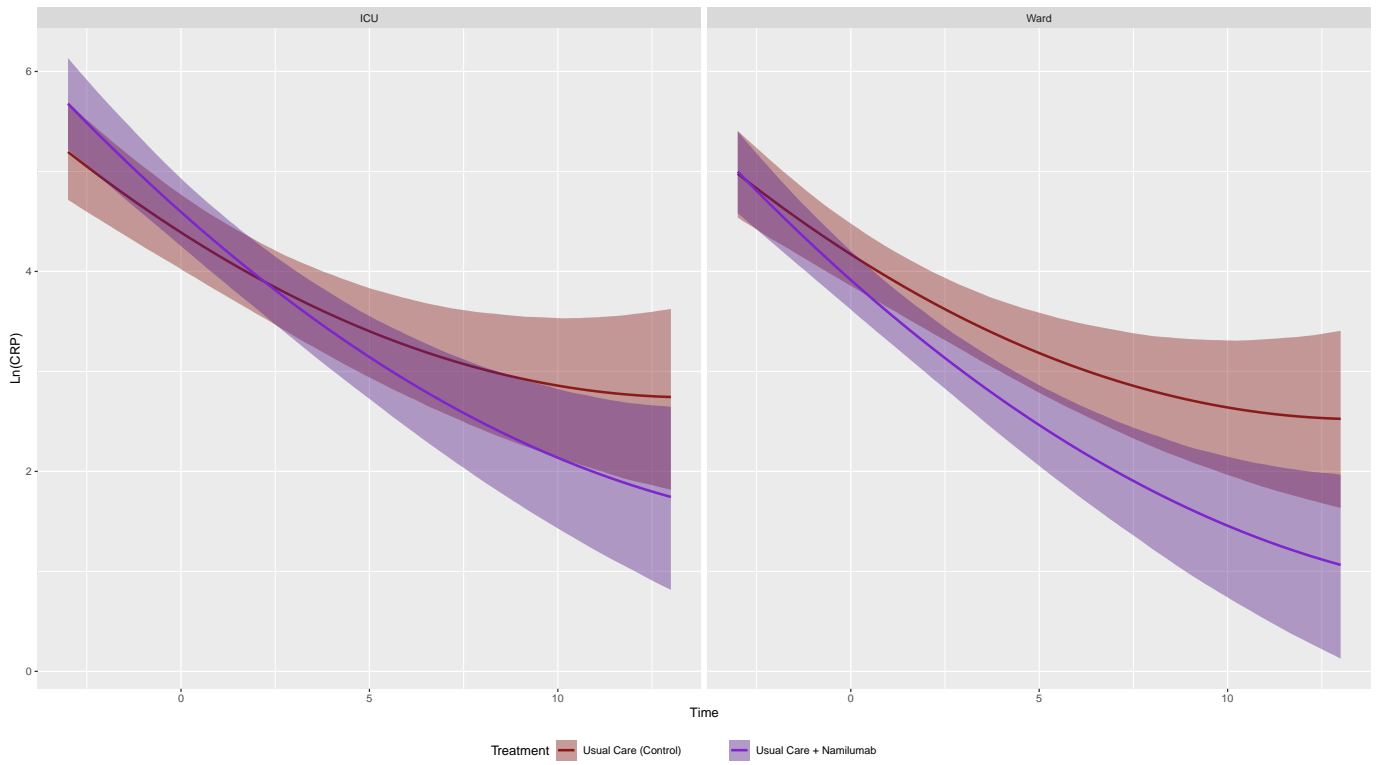
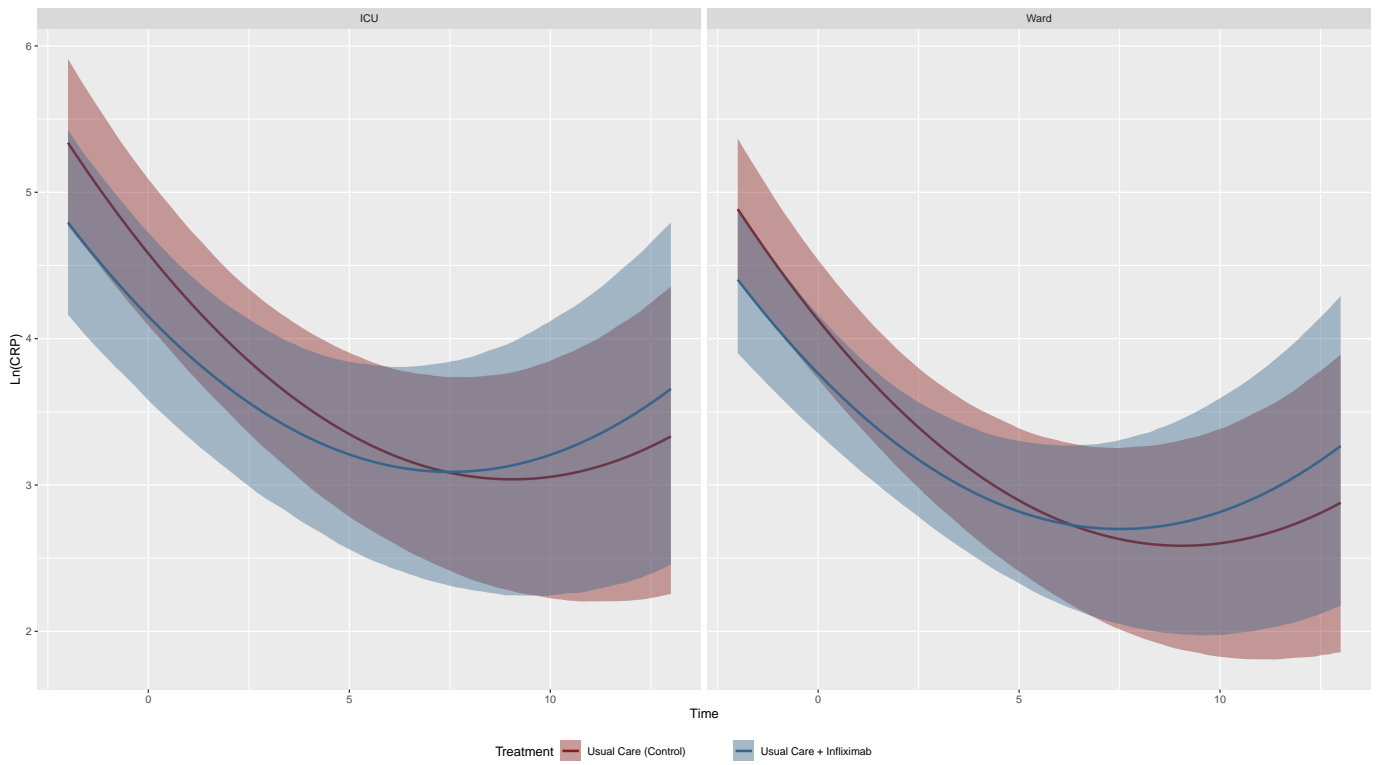


Figure 2.

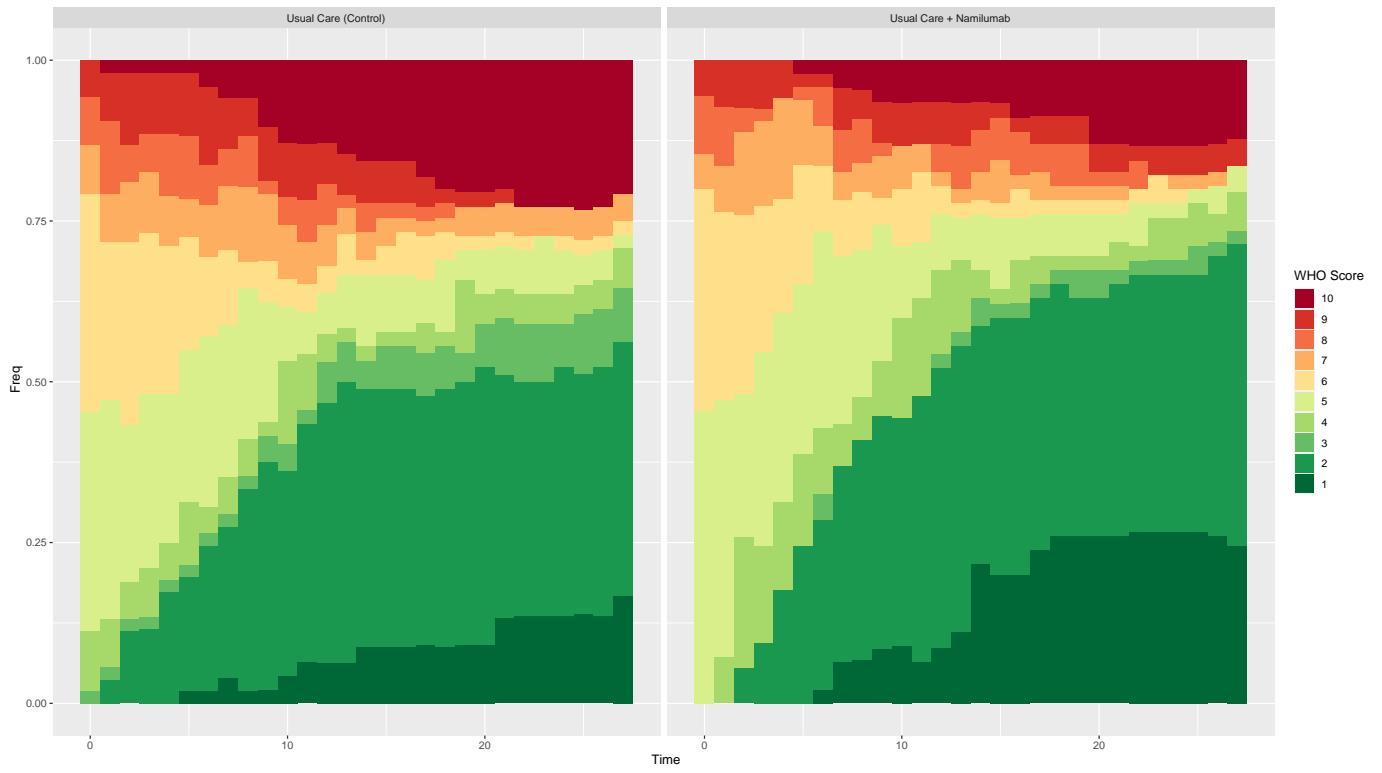


(a)

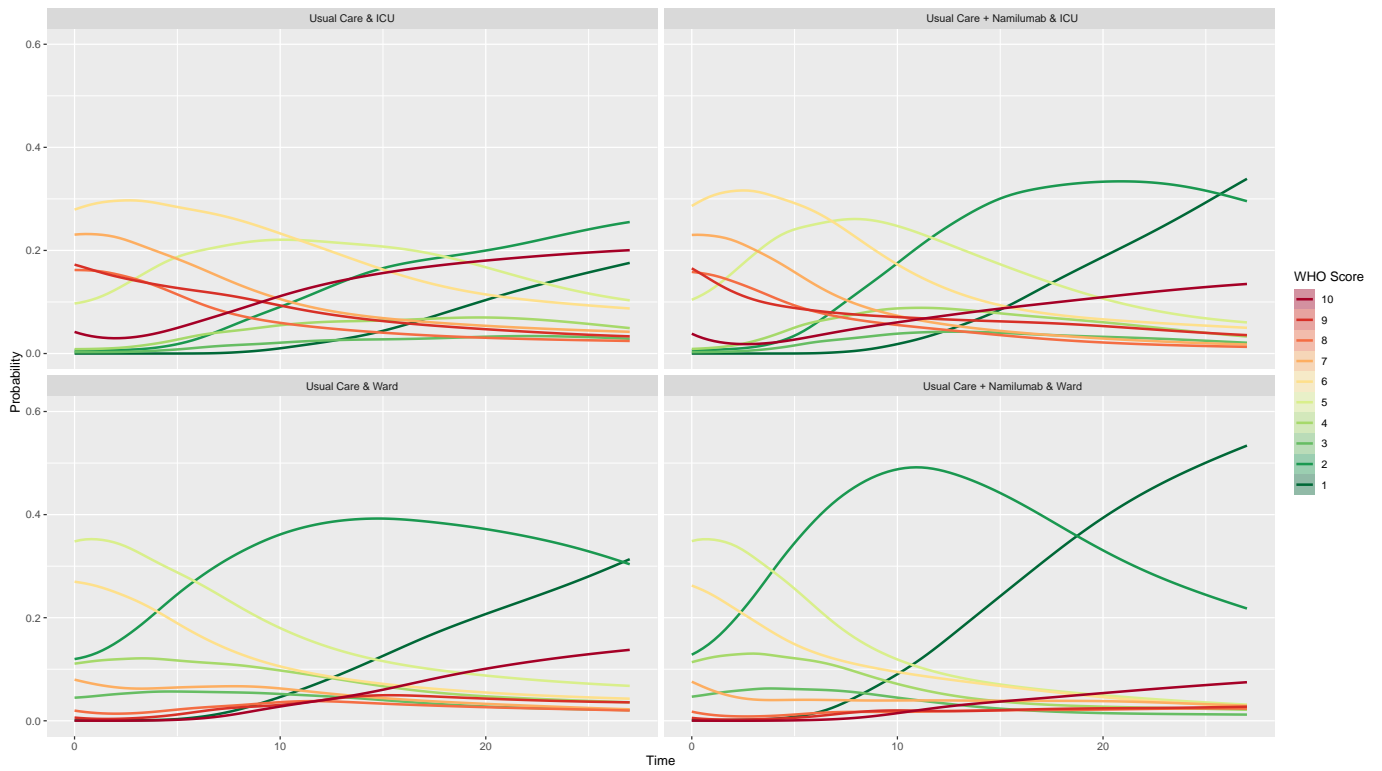


(b)

Figure 3.



(a)



(b)

Supplementary Appendix

Namimumab or infliximab compared to standard of care in hospitalised patients with COVID-19 (CATALYST): a phase 2 randomised adaptive trial

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Supplementary Text Methods

Participant Eligibility

Exclusion criteria included planned palliative care, pregnancy or breastfeeding, women of childbearing potential and non-vasectomised men who were unwilling to use effective contraception for the duration of the trial and throughout the drug-defined post-trial period, known HIV or chronic hepatitis B or C infection, concurrent immunosuppression with biological agents, a history of haematopoietic stem cell or solid organ transplant, known hypersensitivity to drug products or excipients, tuberculosis or other severe infections such as (non-SARS-CoV-2) sepsis, abscesses, and opportunistic infections requiring treatment, moderate or severe heart failure (NYHA class III/IV), or any other indication or medical history, that in the opinion of the patient's local investigator, made the patient unsuitable for trial participation. Co-enrolment into other interventional trials was not permitted with the exception of the RECOVERY-Respiratory Support trial comparing continuous positive airway pressure or high flow nasal oxygen to standard care, as this met current UK guidance on mechanistic independence in co-enrolment.¹⁹

Additional detail on randomisation

The in-house system for randomisation was managed by the programming team at the CRCTU. Site research staff would enter data via eCRFs. The system was designed with the capability of turning off arms or allowing for the addition of new arms given the platform nature of the trial. Programming were to be informed of any modifications to be made following the outcome of interim analyses and implemented them accordingly.

Data Handling

The data was stored securely within a relational database with the raw datasets only accessible by the trials team. Data was entered onto the system at sites through the use of eCRFs. The full details remain in the protocol.

Recommendations

CRP data was considered by the data monitoring committee (DMC) in the context of the emerging safety data to make a recommendation as outlined below:

- a) If there is strong evidence of an additional anti-inflammatory effect (CRP) and a satisfactory safety profile consider progression to clinical endpoint evaluation whether in this trial or in another one;
- b) If there is no evidence of additional biological effect or an unfavourable safety signal, then terminate arm and do not proceed.

Simulations to Inform Sample Size

The simulations and tables below demonstrate the operating characteristics of a trial design with the chosen decision criteria, based on a simpler analysis of the area under the curve for sequential CRP data, with effect sizes informed from a dataset from 1026 hospitalised COVID-19 patients at Queen Elizabeth Hospital, Birmingham. In our simulations, we compared a traditional fixed trial design recruiting 120 patients with candidate adaptive designs. We present basic operating characteristics for the fixed design (Table 6A) and the chosen adaptive design (Table 6B). We studied six scenarios of treatment effect, and estimated, through simulation, the probability of a trial stopping early for "success" or "futility," and ultimately concluding success. Simulations were performed in Fixed and Adaptive Clinical Trial Simulator (FACTS) software using default non-informative priors.

Table A. Operating characteristics for a fixed trial design of 120 patients.

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0	0	0.101	120
A	0	0	0.537	120
B	0	0	0.926	120
C	0	0	0.997	120
D	0	0	0.008	120
E	0	0	0	120

Scenarios A, B, and C are beneficial effects of the intervention with (true) treatment effects of 0.25, 0.5 and 0.75 standard deviations, "null" is zero treatment effect and D and E are harmful effects of 0.25 and 0.5 standard deviations. "success" and "futility" are defined as above.

Table B. Operating characteristics for an adaptive design with interim analyses at 40 and 80 patients.

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0.148	0.624	0.176	66
A	0.455	0.281	0.559	70
B	0.798	0.089	0.890	59
C	0.965	0.012	0.985	48
D	0.03	0.901	0.031	52
E	0.003	0.986	0.003	43

The adaptive design achieves similar probabilities of success in scenarios where the treatment effect is truly beneficial (A, B and C), and increases the probability of success only slightly if the intervention is harmful (D and E). There is some increase in the probability of success if the treatment effect is zero (Type I error) but this is offset by the very substantial reductions in the numbers of patients needed in all scenarios. Moreover, Type I error is not a serious problem as all interventions would be evaluated further in phase III trials.

Additional information on interim analyses

The interim analyses for the DMC were conducted by the trial statisticians. Only the statisticians and the DMC members, who were independent from the operation of the trial, had access to the results in confidence

Supplementary Text Results

Fitted Model – Namilumab

$$\text{Log}(CRP) = 3.41 + a - 0.24 * \text{Time} + b + 0.01 * \text{Time}^2 - 0.22 * \text{CareStatus} + 0.02 * \text{Age} + 0.20 * \text{Trt} - 0.46 * \text{CareStatus} * \text{Trt} - 0.09 * \text{Time} * \text{Trt} + \varepsilon$$

Where

$$a \sim N(0, 0.73^2), b \sim N(0, 0.21^2), \varepsilon \sim N(0, 0.58^2)$$

CareStatus = 1 if on the ward and 0 for ICU, Trt = 1 if receiving Namilumab or 0 if usual care alone

Fitted Model – Infliximab

$$\text{Log}(CRP) = 3.70 + a - 0.34 * \text{Time} + b + 0.02 * \text{Time}^2 - 0.45 * \text{CareStatus} + 0.01 * \text{Age} - 0.43 * \text{Trt} + 0.06 * \text{CareStatus} * \text{Trt} - 0.06 * \text{Time} * \text{Trt} + \varepsilon$$

Where

$$a \sim N(0, 0.79^2), b \sim N(0, 0.18^2), \varepsilon \sim N(0, 0.65^2)$$

CareStatus = 1 if on the ward and 0 for ICU, Trt = 1 if receiving Infliximab or 0 if usual care alone

Supplementary Table 1. Summary of protocol changes

Amendment number	Date of approval	Protocol version number	Type of amendment	Summary of amendment
1	REC: 14-May-20	n/a	Substantial Amendment	Addition of Oxford and UCL as sites
2	MHRA: 29-May-20 HRA: 01-Jun-20	3.0	Substantial Amendment	Addition of two new IMPs: Namilumab and Infliximab. Update SOE, amendments to inclusion/ exclusion criteria. Specifically: New exclusion criteria relating to the addition of the new drugs: <ol style="list-style-type: none"> 1) Known hypersensitivity to drug products or excipients 2) Patients with tuberculosis or other severe infections such as (non-COVID-19) sepsis, abscesses, and opportunistic infections requiring treatment 3) Patients with moderate or severe heart failure (NYHA class III/IV)
3	REC: 10-Jun-20	n/a	Substantial Amendment	Addition of new sites
4	MHRA: 08-Jun-20	n/a	Substantial Amendment	IMPD update
5	MHRA: 12-Jun-20 REC: 12-Jun-20	4.0	Substantial Amendment	Amendment to inclusion criteria. Specifically: Inclusion criterion 1 changed to: 'Hospitalised adult (≥ 16 yrs) patients with a clinical picture strongly suggestive of SARS-CoV-2 pneumonia (confirmed by chest X-ray or CT scan, with or without a positive reverse transcription polymerase chain reaction [RT-PCR] assay)' in order to: <ul style="list-style-type: none"> • Allow CT imaging as evidence for COVID-19 pneumonia • Allow recruitment of patients with strong clinical suspicion for COVID-19 pneumonia but with negative PCR assay Non-substantial amendments to Sample Collection Sub-study text.
6	MHRA: 19-Jun-20 REC: 20-Jun-20	5.0	Substantial Amendment	Amendment to exclusion criteria. Specifically: 'Concurrent immunosuppression with biological agents or prednisone dose $> 20\text{mg}$ ' Was changed to 'Concurrent immunosuppression with biological agents' in order to allow patients to be recruited on dexamethasone, following the RECOVERY data
7	MHRA: 12-Oct-20 REC: 12-Oct-20	6.0	Substantial Amendment	Change of Primary and Secondary Outcomes Specifically: Primary outcome changed to CRP (previously a secondary outcome) from the oxygen saturation to fractional inspired oxygen concentration (SpO ₂ /FiO ₂) ratio, which now becomes a secondary outcome Hospital free days added as a secondary outcome Overall survival listed as a safety measure (previously death included under hospital survival status as a clinical outcome) Applicable changes to Inclusion/ Exclusion Criteria Specifically: Inclusion criteria changed from 'Oxygen saturation (SaO ₂) of $\leq 94\%$ while breathing ambient air or a ratio of the partial pressure of Oxygen (PaO ₂) to the fraction of inspired oxygen (FiO ₂) (PaO ₂ :FiO ₂) ≤ 300 mg Hg ($\leq 40\text{kPa}$)', to 'CRP ≥ 40 ' The following exclusion criteria that relate to the unopened Myelotarg arm were removed from general exclusion and made arm specific: <ul style="list-style-type: none"> • Known veno-occlusive disease • Neutrophil count $< 2 \times 10^9/l$ or White Blood Cell Count $< 4.0 \times 10^9/l$ The following exclusion criteria was removed as it was felt to be unnecessarily hindering recruitment: <ul style="list-style-type: none"> • Chronic Obstructive Pulmonary Disease (known FEV₁ $< 50\%$ predicted or ambulatory or long term oxygen therapy)

				Inclusion of Abbreviations list and eCRF table Update to Statistical Analysis section <ul style="list-style-type: none"> Justification for CRP, operating characteristics and decision rules
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Supplementary Table 2 World Health Organisation Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised; mild disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised; severe disease	Hospitalised; oxygen by NIV or high flow	6
	Intubated and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) and vasopressors, dialysis or ECMO	9
	Death	Dead

Adapted from WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis.* 2020;20:e192-e197.

Footnotes for use in CATALYST

- If pO_2 not available then use the SpO_2/FiO_2 ratio instead
- For pO_2 measurements in kPa, use an online calculator e.g. https://www.msmanuals.com/en-gb/medical-calculators/PaO2_FiO2_Ratio.htm to calculate a pO_2/FiO_2 ratio equivalent to that obtained with pO_2 measured in mmHg, or else consider an equivalent ratio to 200, when dividing pO_2 in kPa by FiO_2 , is 26.7, and an equivalent to 150 is 20.
- If medically fit for discharge, record status as for ambulatory patient
- Asymptomatic implies a return to baseline symptomatic state, i.e. no fever, and no cough, shortness of breath, confusion, myalgia, diarrhoea, fatigue, or weakness above what the participant would have experienced on a daily basis before their COVID-19 episode
- Symptomatic but independent, implies that the participant has some of the additional symptoms as above, but needs no additional help with activities of daily living above what they required prior to their COVID-19 episode.
- Symptomatic but needs assistance, implies that in addition to having symptoms as above, they require help with activities of daily living i.e. bathing/showering, personal hygiene and combing of hair, dressing, toileting, mobility/transferring and self-feeding, above what they required on a daily basis prior to their COVID-19 episode.
- Score 0 (uninfected: no viral RNA detected) is not being assessed as part of CATALYST.

Supplementary Table 3. Point estimates and associated 95% credible intervals for mean posterior predictive expected ln(CRP) values on days 1, 7 and 14 for ward and ICU patients allocated to usual care alone or namilumab plus usual care and for the differences between these groups (Δ). Conditional effects data derived from Bayesian multi-level regression.

Care Status	Day	Usual Care (Control)	Usual Care + Namilumab	Δ
Intensive Care Unit	1	4.39 (4.02, 4.77)	4.59 (4.25, 4.93)	0.2 (-0.3, 0.7)
Intensive Care Unit	7	3.26 (2.75, 3.73)	2.91 (2.44, 3.37)	-0.35 (-1.02, 0.35)
Intensive Care Unit	14	2.74 (1.82, 3.62)	1.74 (0.82, 2.65)	-1.00 (-2.26, 0.26)
On Ward	1	4.17 (3.86, 4.48)	3.91 (3.62, 4.21)	-0.26 (-0.67, 0.17)
On Ward	7	3.04 (2.60, 3.49)	2.23 (1.77, 2.68)	-0.81 (-1.45, -0.18)
On Ward	14	2.53 (1.64, 3.41)	1.06 (0.13, 1.97)	-1.96 (-4.92, 0.79)

Supplementary Table 4. Point estimates and associated 95% credible intervals for mean posterior predictive expected ln(CRP) values on days 1, 7 and 14 for ward and ICU patients allocated to usual care alone or infliximab plus usual care and for the differences between these groups (Δ). Conditional effects data derived from Bayesian multi-level regression.

Care Status	Day	Usual Care (Control)	Usual Care + Infliximab	Δ
Intensive Care Unit	1	4.58 (4.09, 5.09)	4.15 (3.58, 4.72)	-0.43 (-1.19, 0.32)
Intensive Care Unit	7	3.21 (2.62, 3.80)	3.13 (2.44, 3.81)	-0.08 (-0.99, 0.82)
Intensive Care Unit	14	3.33 (2.26, 4.35)	3.66 (2.46, 4.79)	0.32 (-1.19, 1.77)
On Ward	1	4.13 (3.72, 4.54)	3.76 (3.35, 4.16)	-0.37 (-0.94, 0.20)
On Ward	7	2.76 (2.23, 3.30)	2.74 (2.19, 3.27)	-0.02 (-0.79, 0.73)
On Ward	14	2.88 (1.86, 3.89)	3.27 (2.17, 4.29)	0.52 (-2.15, 2.94)

Supplementary table 5. Point estimates of the probability of being at each level of the WHO Clinical progression score on days 1, 14 and 28 for ward and ICU patients allocated to usual care alone or namilumab plus usual care. Conditional effects data derived from Bayesian longitudinal proportional odds ordinal regression.

	Care Status	Day	WHO score level									
			1	2	3	4	5	6	7	8	9	10
Usual Care (Control)	Intensive Care Unit	1	0.00	0.01	0.00	0.01	0.10	0.28	0.23	0.16	0.17	0.04
	Intensive Care Unit	14	0.03	0.13	0.03	0.06	0.22	0.20	0.08	0.05	0.07	0.14
	Intensive Care Unit	28	0.18	0.26	0.03	0.05	0.10	0.09	0.04	0.02	0.03	0.19
	On Ward	1	0.00	0.12	0.04	0.11	0.35	0.27	0.08	0.02	0.01	0.00
	On Ward	14	0.09	0.39	0.05	0.08	0.14	0.08	0.05	0.04	0.04	0.04
	On Ward	28	0.31	0.31	0.02	0.04	0.07	0.04	0.02	0.02	0.03	0.14
Usual Care + Namilumab	Intensive Care Unit	1	0.00	0.01	0.00	0.01	0.10	0.29	0.23	0.16	0.16	0.04
	Intensive Care Unit	14	0.06	0.26	0.04	0.09	0.21	0.12	0.05	0.04	0.07	0.08
	Intensive Care Unit	28	0.34	0.30	0.02	0.03	0.06	0.05	0.02	0.01	0.03	0.13
	On Ward	1	0.00	0.12	0.05	0.12	0.35	0.26	0.07	0.02	0.01	0.00
	On Ward	14	0.18	0.48	0.03	0.05	0.08	0.07	0.04	0.02	0.02	0.03
	On Ward	28	0.54	0.22	0.01	0.02	0.03	0.03	0.03	0.02	0.03	0.07

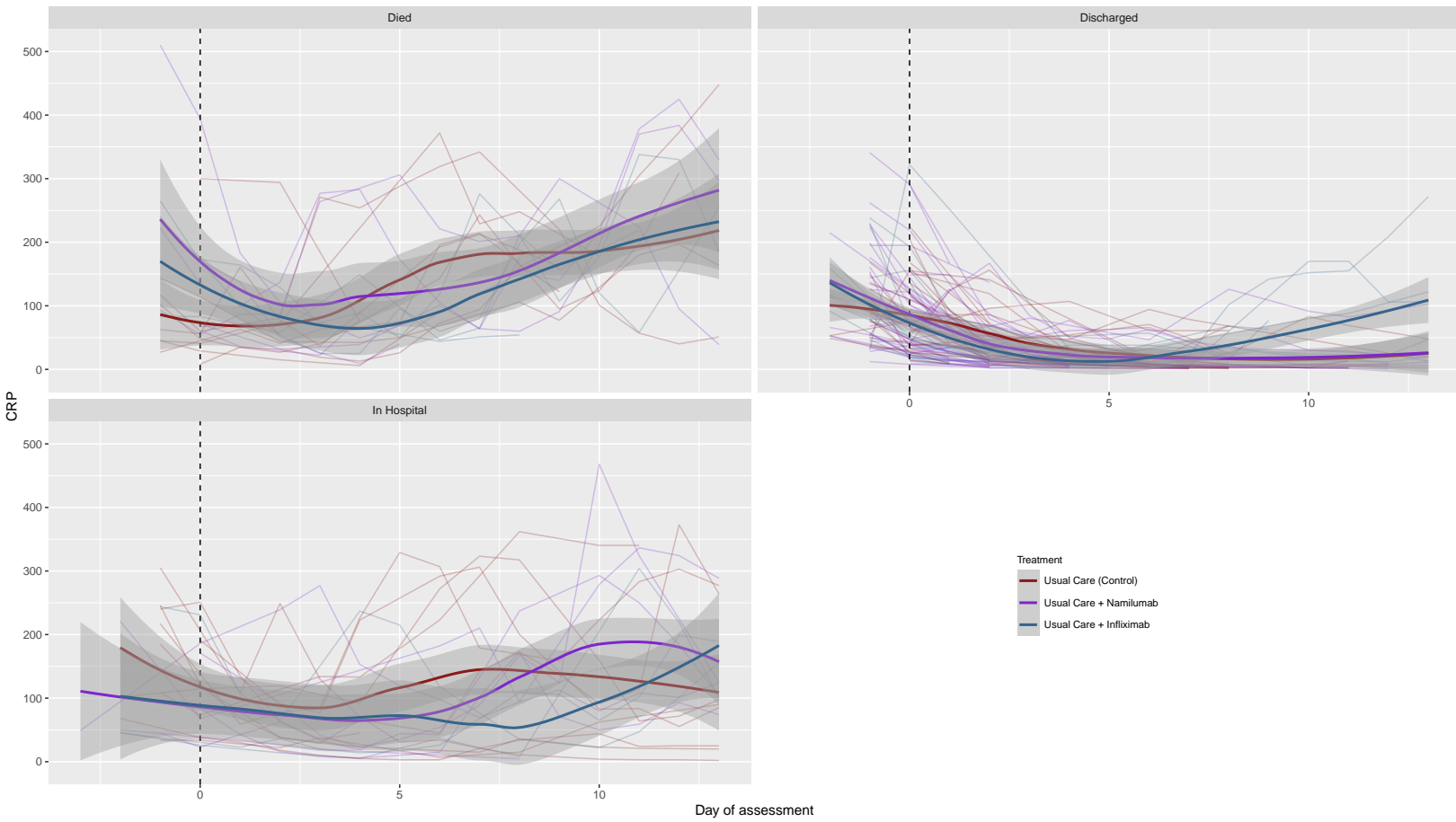
Supplementary table 6. Point estimates of the probability of being at each level of the WHO Clinical progression score on days 1, 14 and 28 for ward and ICU patients allocated to usual care alone or infliximab plus usual care. Conditional effects data derived from Bayesian longitudinal proportional odds ordinal regression.

	Care Status	Day	WHO score level									
			1	2	3	4	5	6	7	8	9	10
Usual Care (Control)	Intensive Care Unit	1	0.00	0.00	0.00	0.01	0.06	0.21	0.26	0.25	0.14	0.07
	Intensive Care Unit	14	0.03	0.15	0.07	0.08	0.18	0.18	0.09	0.05	0.04	0.14
	Intensive Care Unit	28	0.21	0.28	0.06	0.05	0.07	0.08	0.04	0.02	0.01	0.17
	On Ward	1	0.00	0.09	0.09	0.13	0.28	0.27	0.10	0.02	0.00	0.00
	On Ward	14	0.11	0.42	0.09	0.07	0.09	0.05	0.04	0.05	0.04	0.03
	On Ward	28	0.40	0.28	0.04	0.03	0.04	0.02	0.02	0.02	0.01	0.13
Usual Care + Infliximab	Intensive Care Unit	1	0.00	0.00	0.00	0.01	0.08	0.23	0.26	0.24	0.12	0.05
	Intensive Care Unit	14	0.02	0.12	0.05	0.07	0.18	0.19	0.10	0.07	0.04	0.15
	Intensive Care Unit	28	0.16	0.24	0.06	0.06	0.09	0.09	0.05	0.04	0.02	0.19
	On Ward	1	0.00	0.12	0.10	0.14	0.29	0.25	0.08	0.02	0.00	0.00
	On Ward	14	0.09	0.39	0.10	0.08	0.10	0.07	0.05	0.04	0.04	0.05
	On Ward	28	0.31	0.31	0.05	0.04	0.05	0.04	0.02	0.02	0.02	0.14

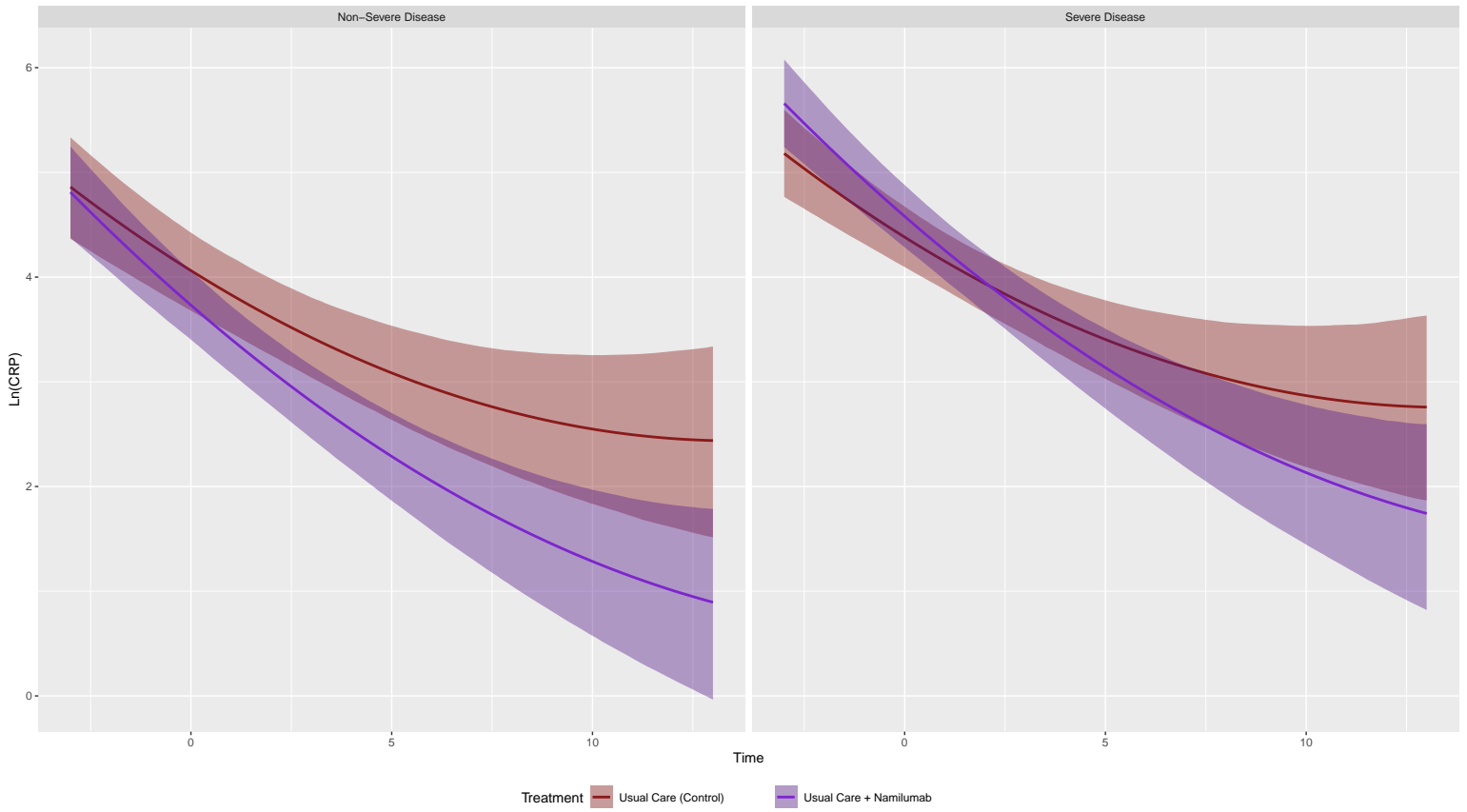
Supplementary Table 7. Total recorded adverse events, SAEs and deaths due to any cause. Specific diagnoses relate to adverse events that are CTCAE grade ≥ 3 , secondary infection or allergic reaction. Only events occurring at least twice within an active drug/usual care comparison are shown. Data shown are number of adverse event occurrences (number of patients affected) in the safety population.

	Namilumab		Infliximab	
	Usual care n=54	Active arm n=55	Usual care n=34	Active arm n=29
Total reported adverse events (all grades)	145 (29)	134 (30)	112 (17)	102 (20)
Total adverse events (CTCAE grade ≥ 3, secondary infection or allergic reaction)	115 (24)	132 (25)	102 (16)	79 (16)
Total infection events	10 (7)	20 (8)	7 (4)	4 (4)
SAEs	10 (10)	10 (10)	5 (5)	6 (6)
Deaths	10 (10)	6 (6)	5 (5)	4 (4)
Anaemia	10 (6)	10(6)	8 (5)	2 (2)
Sinus bradycardia	2 (1)	0 (0)	2 (1)	0 (0)
Multorgan failure	3 (3)	1 (1)	-	-
Covid pneumonia/pneumonitis	5(5)	4(4)	2 (2)	2 (2)
Lung infection	2(2)	1(1)	-	-
Pleural infection	2(1)	0(0)	2 (1)	0 (0)
Sepsis	1(1)	2(2)	-	-
Raised ALT	3(3)	5(5)	1 (1)	1 (1)
Raised Troponin I	0(0)	2(1)	-	-
Raised Creatinine	2(2)	4(3)	2(2)	2(1)
Raised CRP	5(4)	2(2)	5(4)	0(0)
Raised d-dimers	6(5)	3(3)	5(4)	1(1)
Raised ferritin	7(6)	5(5)	5(4)	11(7)
Low lymphocytes	16(12)	5(3)	11 (8)	4 (2)
Raised monocytes	0(0)	3(2)	-	-
Raised neutrophils	9(5)	5(3)	9 (5)	4 (4)
Raised white cells	9(6)	7(4)	9 (6)	9 (5)
Low platelets	1(1)	1(1)	-	-
Raised urea	9(7)	11(5)	8(6)	8(5)
Raised potassium	6(5)	1(1)	4(3)	2(1)
Raised sodium	1(1)	2(1)	-	-
Raised triglycerides	3(3)	1(1)	2(2)	6(4)
Low albumin	15 (13)	11 (7)	12 (10)	13 (8)
Low sodium	2(2)	1(1)	2(2)	2(2)
ARDS	-	-	1(1)	1(1)
Hypotension	-	-	0(0)	2(2)

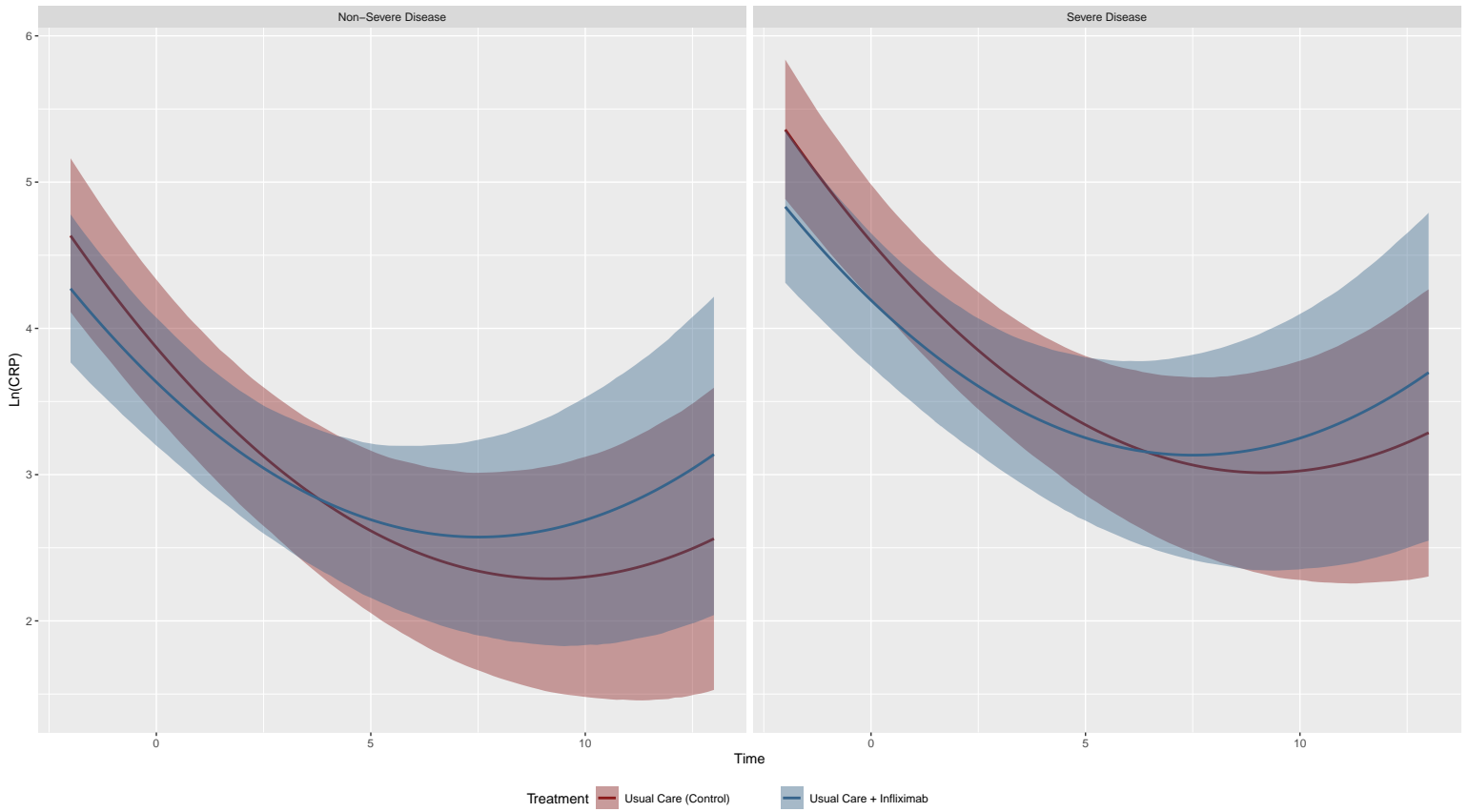
Supplementary Figure 1. CRP over time in relation to day 28 outcomes of death, discharge, and ongoing hospitalisation within the whole CATALYST modified intention to treat population.



Supplementary Figure 2. Conditional effects plots of CRP modelled over time in patients recruited in with non-severe and severe disease at baseline for namilumab (A) and infliximab (B). Severe disease was defined as the use of non-invasive or invasive ventilation or high flow nasal oxygen at baseline. Time 0 is day 1 of assessment.

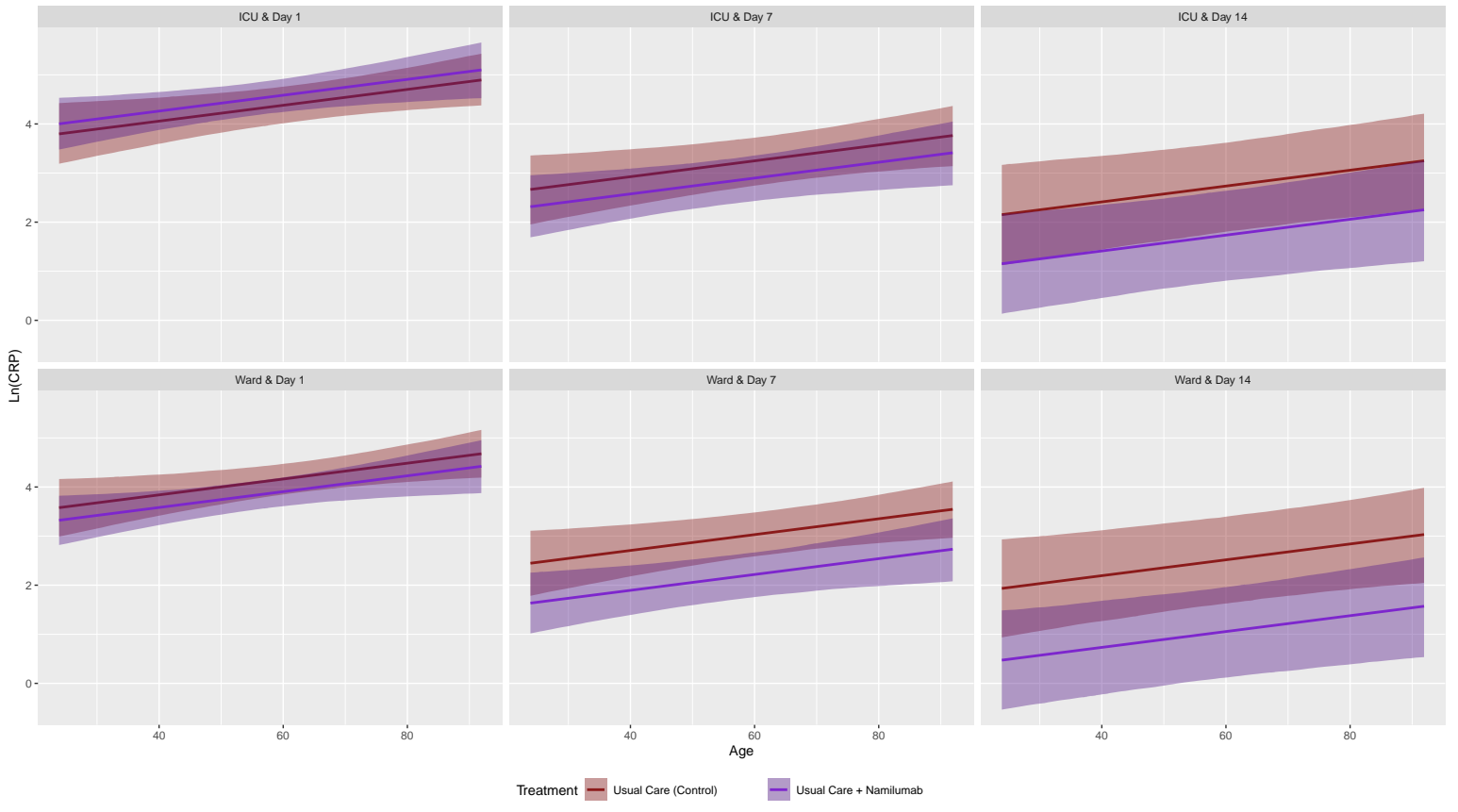


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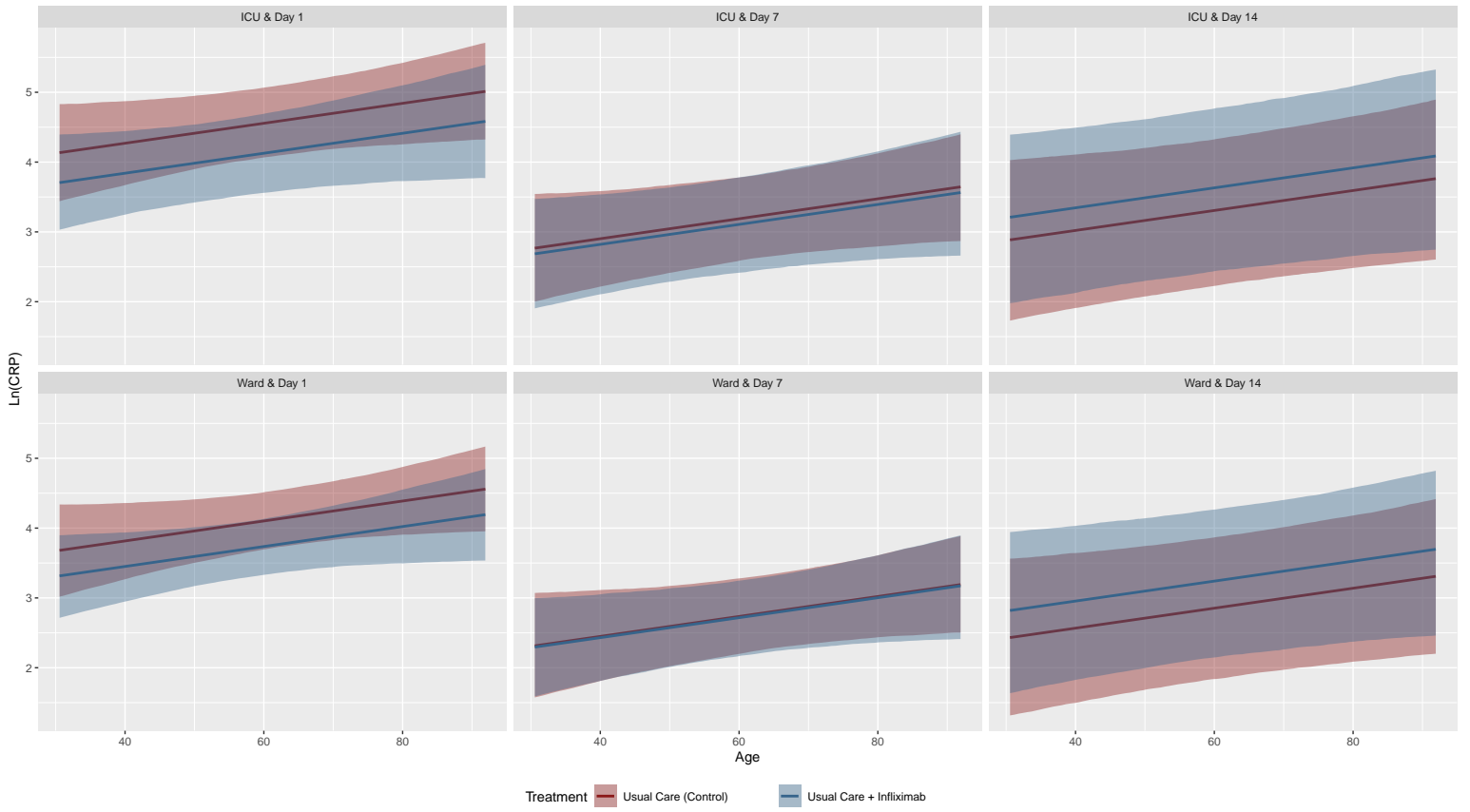


(b)

Supplementary Figure 3. Conditional effects model of CRP in relation to age and treatment at days 0, 7 and 14 in ward and ICU groups. CRP is associated with age but the effect of (A) namilumab and (B) infliximab on CRP is independent of age.

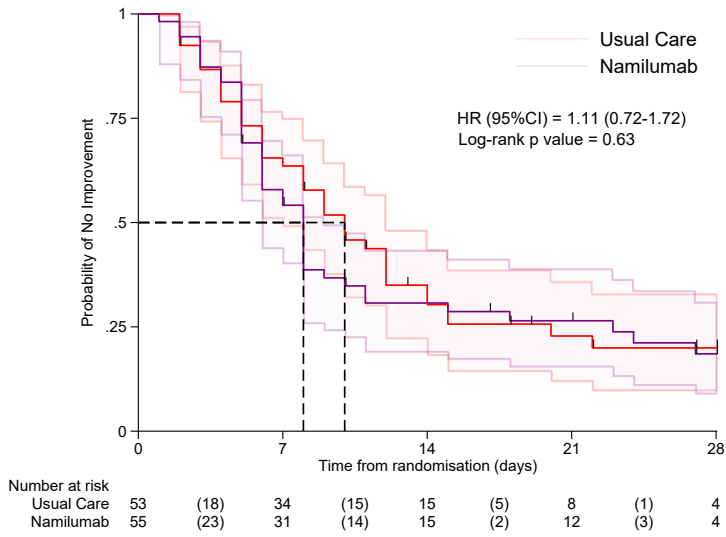


(a)

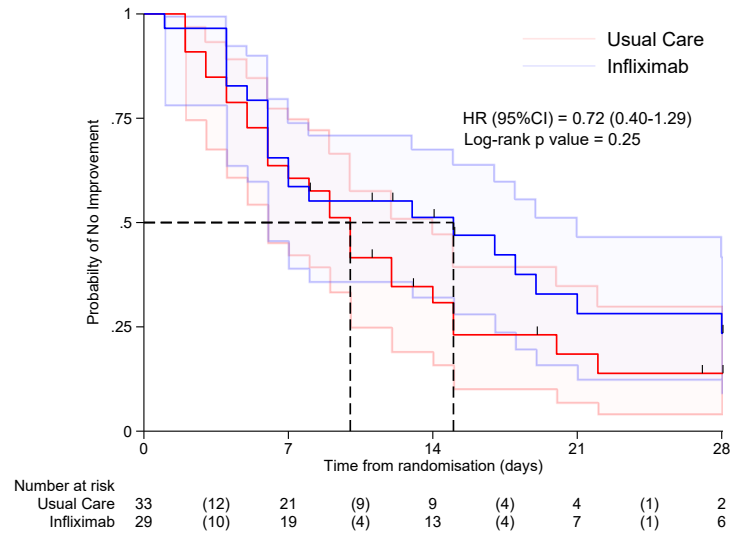


(b)

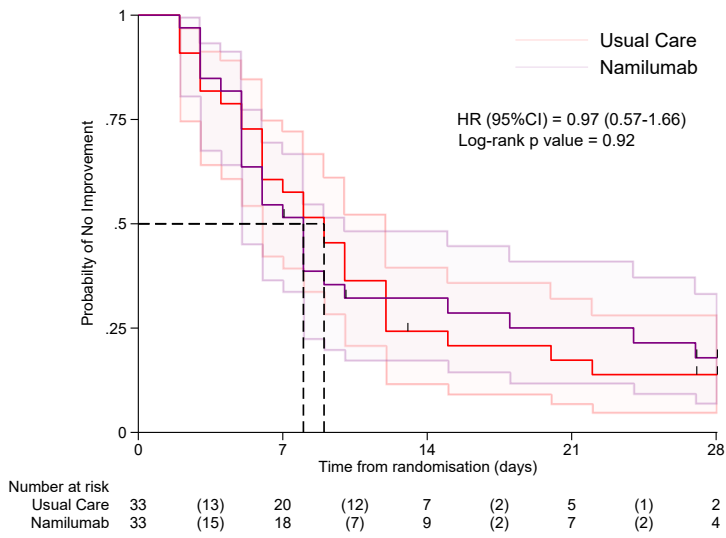
Supplementary Figure 4. Kaplan-Meier plots for time to 2 point improvement for whole population (A, B), ward (C, D) and ICU (E, F) for namilumab (A, C, E) and infliximab (B, D, F).



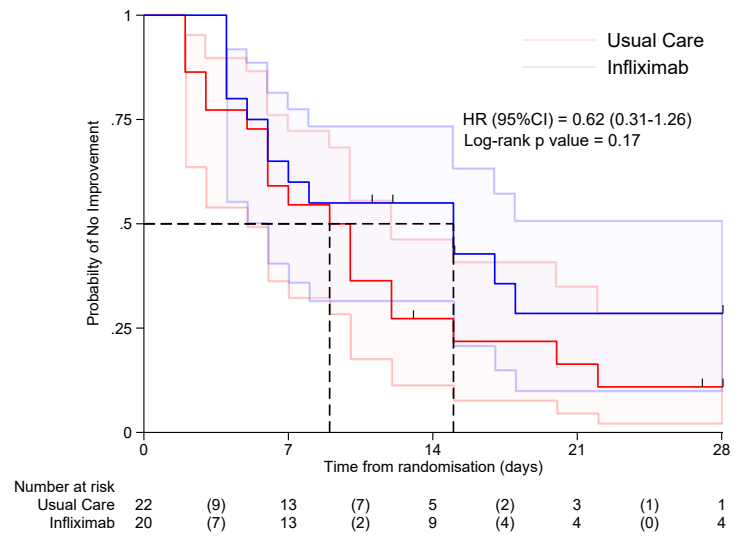
(a)



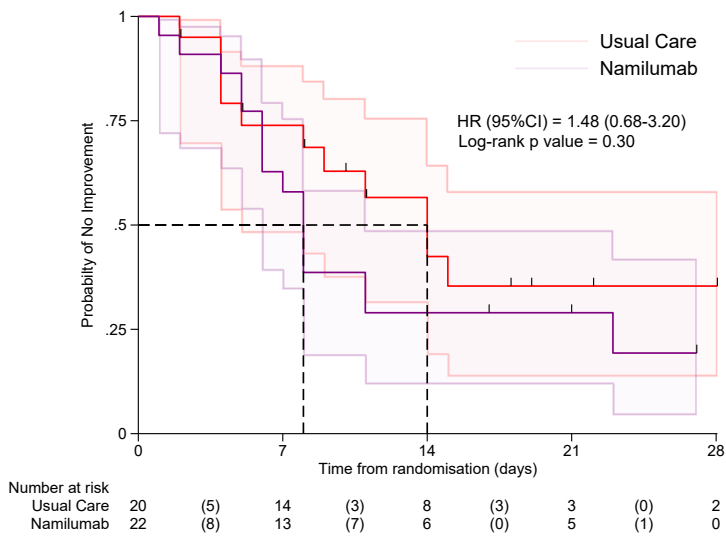
(b)



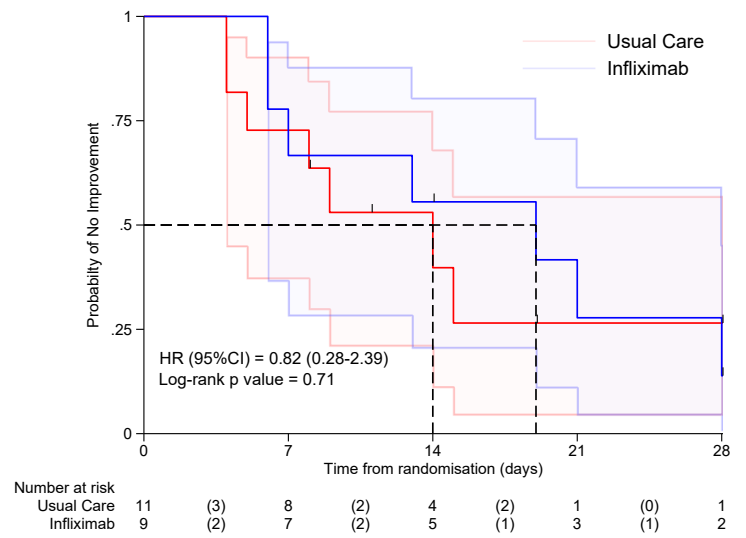
(c)



(d)

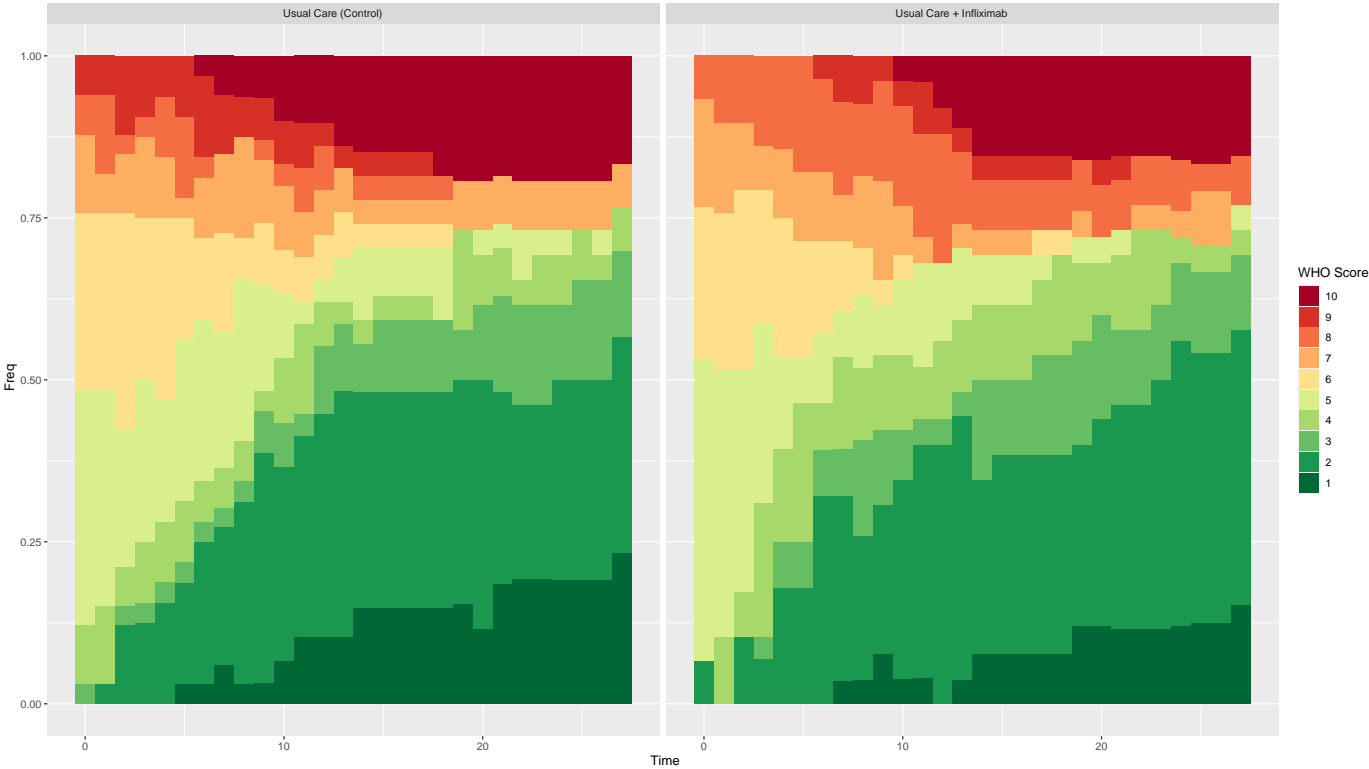


(e)

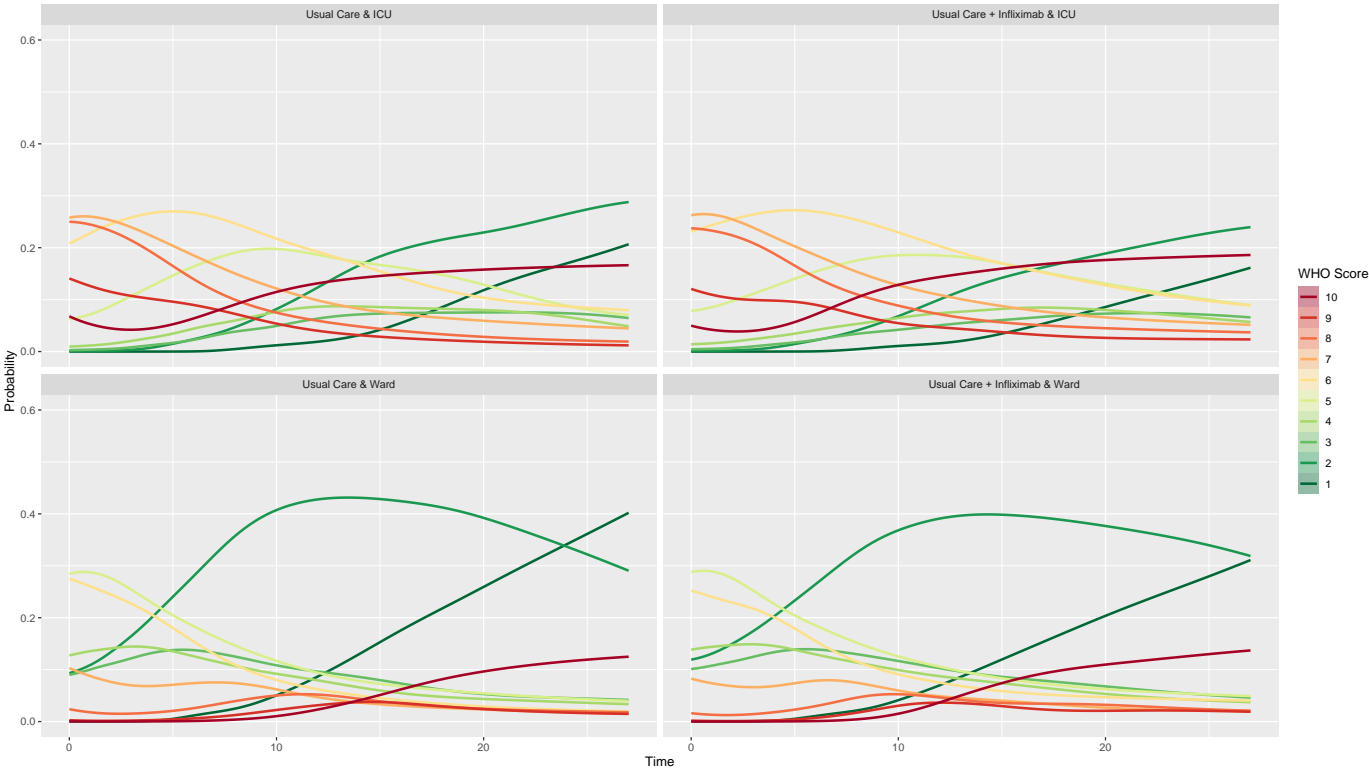


(f)

Supplementary Figure 5. WHO clinical progression score over 28 days for usual care versus infliximab. A, stacked bar chart of raw data for whole population eligible for comparison. B, conditional effects plots of WHO score modelled over time in days showing the probability of being at each level on each day for patients recruited in ICU and ward.

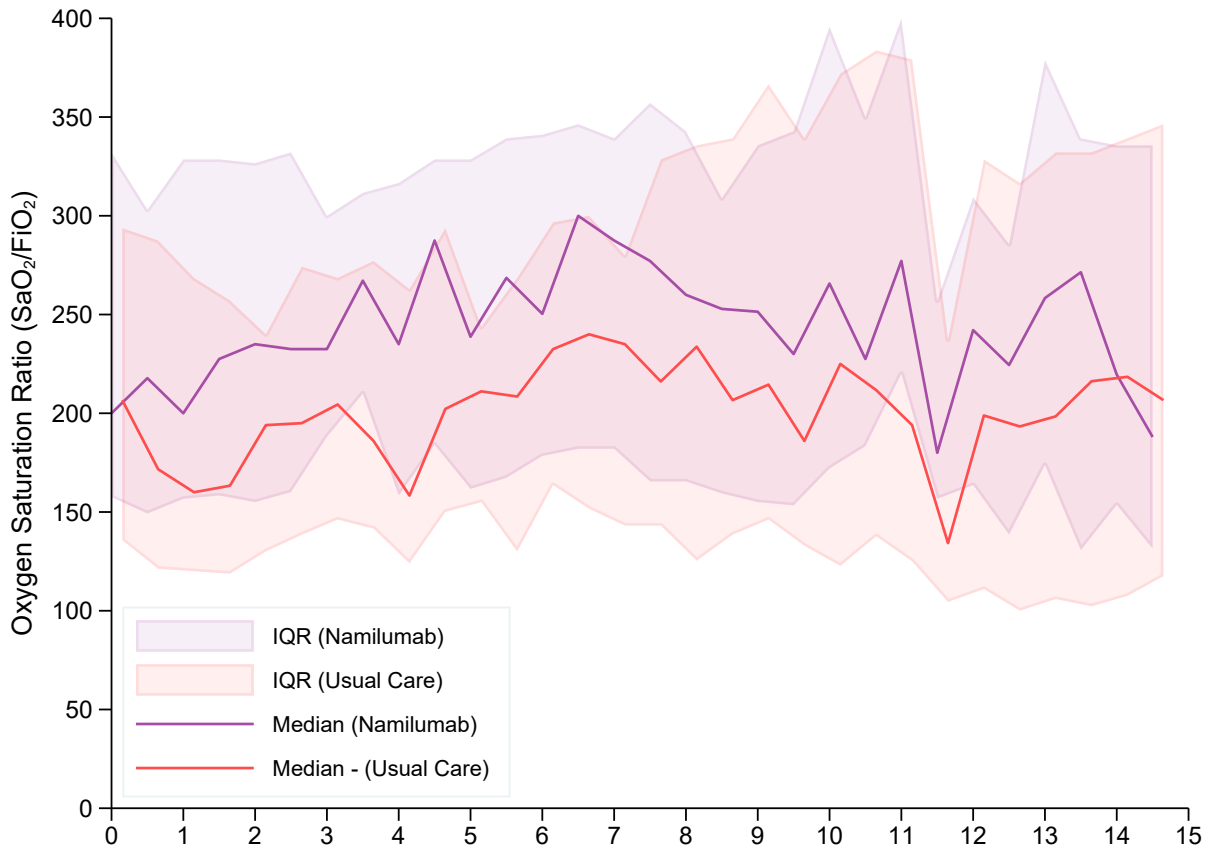


(a)

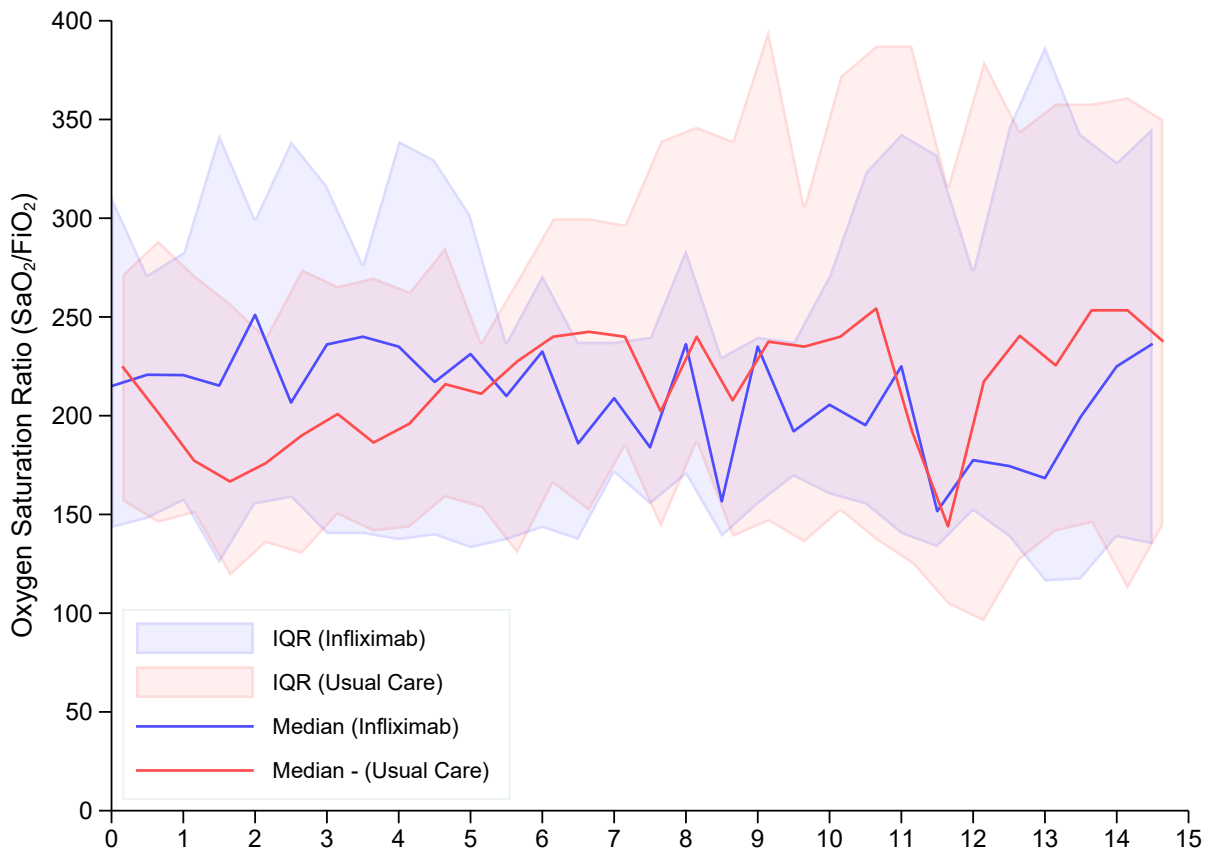


(b)

Supplementary Figure 6. Median oxygen saturation to fraction of inspired oxygen ratio (SF ratio) over time (days) for (A) namilumab (n=55 namilumab and n=54 usual care) and (B) infliximab (n=34 usual care and n=29 infliximab). Higher values indicate better oxygenation status.



(a)





Statistical Analysis Plan

A randomised phase II proof of principle multi-arm multi-stage trial designed to guide the selection of interventions for phase III trials in hospitalised patients with COVID-19 infection.

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Document Control Sheet:

Statistical Analysis Plan version:	Reason for update:
v1.0	Initial Version
v2.0	Incorporation of joint-modelling and AUC approach for the primary analysis, complimentary analyses to attempt to take account of censoring. Addition of ITT analysis for secondary endpoints and MITT definition for secondary endpoints. Modification of primary analysis to state inference will be based on only the interaction term of the model. Specification of subgroup analyses based on disease severity, a request of the DMC.

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1 INTRODUCTION

1.1 Purpose of the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) provides guidelines for the analysis and presentation of results for the Catalyst trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Documentation' section of the Trial Master File. The statistical analysis will be carried out by the trial Statisticians.

1.2 Summary of the Trial

Trial Design

Catalyst is a rapid, open-label, phase II, multi-arm, multi-stage trial permitting an efficient evaluation of the potential efficacy of these targeted drugs which can then be considered for larger-scale testing by one of the current national platform trials.

Objectives

Primary Objectives

- To investigate whether candidate treatments demonstrate evidence of greater attenuation of inflammation as defined by an improvement in C-reactive protein (CRP) concentrations compared with usual care in COVID-19 patients.
- To recommend drugs that should be evaluated further in one of the phase III trials.

Outcome Measures

Primary Outcome Measures

- C-reactive protein measured over time up to day 14 for each patient.

Secondary Outcome Measures

- World Health Organisation (WHO) Clinical Progression improvement Scale (1-10 scale; for the purposes of this trial level 0, no viral RNA detected, will not be assessed)
- The ratio of the oxygen saturation to fractional inspired oxygen concentration (SpO₂/FiO₂), measured from randomisation to day 14, hospital discharge or death. SpO₂ and FiO₂ are measured as part of routine clinical care
- Respiratory rate
- Body temperature
- NEWS-2 score
- Length of hospital stay
- Hospital survival status at day 28 / hospital free days
- Proportion of patients discharged at day 28
- Destination of discharge
- Lymphocyte and Neutrophil counts and ratios
- Ferritin, D-Dimer and LDH
- Adverse events (AEs) and Serious Adverse Events (SAEs) as recorded by Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 of grade ≥ 3 with interest in veno-occlusive disease (VOD), secondary infection and allergic reaction
- Overall Survival

Exploratory Outcome Measures

- Blood inflammatory mediators, biomarkers, transcriptome and cellular immunology in relation to COVID-19 infection
- Viral load
- Host DNA assessed at baseline to assess for predictors of disease severity and drug response
- blood biomarkers of aveolar epithelial cell damage to include surfactant D and RAGE

Patient Population

This trial seeks to recruit hospitalised patients with COVID-19 who are hypoxic, admitted to either a hospital ward or ICU, and are at risk of deterioration.

Sample Size

A total of up to 60 patients per treatment arm will be recruited.

2 TIMING AND REPORTING OF INTERIM AND FINAL ANALYSES

There two planned interim analyses for the primary endpoint at n=20 and n=40 per arm respectively. Data analyses pertaining to trial conduct, data quality and patient safety will be supplied in confidence to an independent DMC throughout the period the trial is running. The DMC shall review the available data on a proposed 3 monthly basis.

The final analyses for the trial will be conducted once the end of trial has been reached. The final analyses will incorporate the primary, secondary and all exploratory outcomes as detailed in this analysis plan. The end of trial is defined as 6 months after the last data capture.

3 RECRUITMENT AND RANDOMISATION

3.1 Recruitment

At the point of analysis the following data will be reported:

- Date of the database snapshot used for recruitment analysis
- Total number of patients who have been recruited into the trial and randomised to each treatment arm
- Recruitment over time (monthly and cumulative)
- Recruitment by site

3.2 Randomisation

Patients will be randomised 1:1 between Usual Care (Control Arm) and interventional arms using the minimisation procedure described by Pocock and Simon, with a single stratification variable with two levels; Care status: 'On ward' or 'ICU'. Patients will be randomised into either a control group or to receive interventional treatments that are available at their site.

3.3 Ineligible Patients

Ineligible patients are defined as those registered patients who are subsequently found to not meet the eligibility criteria of the trial after being recruited. The proportion of ineligible patients and reasons for their ineligibility will be reported for each treatment arm. In addition the number of patients who were screened in total will be reported along with the number of patients not recruited to the trial and their associated reasons e.g. ineligible.

4 DATA QUALITY

4.1 Data Quality: CRFs

Patient data is collected using case report forms (CRFs) and electronic case report forms (eCRFs). Data collected in this way will be stored on a trial database. The trial database will be checked for missing data and any discrepancies at least annually but prior to any analysis as according to the trial specific data validation plan, which will be developed by both the trial statisticians and the trial coordinator.

4.2 Return Rates: CRFs

The proportion of returned CRFs compared to those that were expected will be reported for each case report form.

5 TRIAL POPULATION

5.1 Patient Characteristics

A summary of patient characteristics will be reported. Descriptive statistics will be provided in the summary including counts and percentages for categorical data items and mean (sd), median and ranges for continuous data items.

5.2 Definition of Populations for Analysis

Safety Population - Safety population will include all patients who receive any trial treatment. For interventional arms this requires the patient to have received some IMP.

MITT Population - The Modified Intention-To-Treat population for the primary analyses will include all patients who receive any trial treatment and who have a baseline CRP measurement and at least one further CRP measurement post baseline. For the secondary endpoints, this includes all patients who receive any trial treatment and have available data for the respective outcome measure.

ITT Population - This includes all randomised patients in their treatment arms, that have available data for the respective outcome measure.

6 TREATMENT RECEIVED

For each treatment arm, the proportion of participants who received treatment as per protocol will be reported. The proportion of participants who discontinued treatment early will also be reported along with a tabulation of the reasons. Summary statistics for all participants on treatment arms will be reported e.g. median/mean time on treatment, these statistics will be tailored for the specific arms as naturally the treatments may widely differ and thus different summary measures will be relevant.

7 SAFETY ANALYSIS

The number of serious adverse events (including SARs and SUSUARs), and the number of treatment-related deaths will be reported for each treatment arm. The reporting period for Adverse Events/Serious Adverse Events (SAE's) will commence from the date of consent. Safety will be assessed by looking at adverse events (CTCAE).

The following details will be reported for each treatment arm for all patients who are part of the safety population:

- Adverse events at baseline, summarised by event and number of patients experiencing such events.
- Max grade experienced for all patients.
- A summary of number of events and patients for all toxicities by event and grade.
- The number of events and patients for all grades of toxicities.
- All serious adverse events will be reported, details to be presented include but are not limited to; admitting event, other events, reason for SAE, outcome, sequel and relatedness.

8 ANALYSIS

For all analyses data will be analysed for each intervention against the control group, including in each analysis only those participants who were eligible for the those treatment arms at the point of randomisation. The primary analysis will be conducted on the MITT population and all secondary analyses will be conducted on both the MITT population and ITT unless otherwise specified.

New intervention arms may be added as new interventions become available. All comparisons will be performed temporally with regards to control arm data.

8.1 Analysis of Primary Outcome Measure

The CRP data will be modelled using Bayesian multi-level models that allow for nesting of the repeated measures data within patient, and allowing for non-linear responses. This approach will facilitate an assessment of the effects of the treatments on the CRP. Specifically, posterior probabilities for the treatment/time interaction term will be used to conduct decision making. Care status as a randomisation stratification factor will be incorporated accordingly into the model structure along with age as a known prognostic indicator.

At the specified decision points, with interim analyses at $n=20$ and $n=40$ and a final analysis at $n=60$ per arm, the CRP data will be considered in the context of the emerging safety data to make a recommendation as outlined below:

- a) If there is strong evidence of an additional anti-inflammatory effect (CRP) and a satisfactory safety profile consider progression to clinical endpoint evaluation whether in this trial or in another one
- b) Terminate arm and do not proceed (based on lack of evidence of an additional biological effect or of an unfavourable safety signal)

We will define that ‘strong evidence’ or ‘success’ will be if there is an 90% probability that the intervention arm is better than usual care in reducing CRP as seen by the treatment/time interaction covariate. ‘lack of evidence’ or ‘futility’ is defined as less than 50% probability of the intervention being better than usual care. However, given the large number of agents being investigated in various phase II trials, the size of effect and the totality of data will be reviewed before recommending adoption by a phase III platform.

In addition to the above analysis we will analyse the data using two further approaches, namely, modelling AUC and an additional joint-modelling approach for CRP and discharge/death, this is to ascertain if censoring events for CRP; discharge/death, have had any impact on inference and if so to model accordingly.

8.2 Analysis for Secondary Outcome Measures

Outcome measures

- World Health Organisation (WHO) Clinical Progression improvement Scale
 - Time to improvement, measured from the date of randomisation, an event here is defined as at least a one-point improvement on the Time to Clinical Improvement Scale. A Kaplan-Meier plot will be produced for each treatment and control arm comparison, estimates of median time to improvement will be reported along with associated confidence intervals (where they can be estimated). In addition to the one-point improvement an additional analysis utilising a two-point improvement will be conducted, to be comparable with other studies.
 - Patients’ scores on the Clinical Improvement Scale for each day will be displayed graphically, and modelled using Bayesian longitudinal ordinal regression, as described by Harrell (<http://hbiostat.org/proj/covid19/bayesplan.html>).
- The ratio of the oxygen saturation to fractional inspired oxygen concentration (SpO_2/FiO_2) will be presented graphically over time.
- Length of hospital stay will be summarised via descriptive statistics, stratified by treatment group. Reasons for such lengths of stay will be reported and summarised accordingly.
- Respiratory rate, body temperature and NEWS-2, will be plotted over time and summarised through descriptive statistics. These measures may also be modelled over time using multilevel modelling. Exploratory data analysis will drive model formulation, assumptions will be tested accordingly. All modelling will be exploratory in nature.
- The proportion of patients discharged at day 28 along with destination of discharge will be presented accordingly.
- Hospital survival status at 28 days will be reported as a tabulation of the proportion of patients who have died, been discharged or are still in hospital by day 28. Hospital-free days will be summarised through descriptive statistics, patients still in hospital or who have died will be incorporated having 0 hospital-free days.

- Lymphocyte, neutrophil and full blood counts with lymphocyte: neutrophil ratios and ferritin, D-Dimer and Triglycerides LDH values will be plotted over time and summarised through descriptive statistics. These measures may also be modelled over time using multilevel modelling. Exploratory data analysis will drive model formulation, assumptions will be tested accordingly. All modelling will be exploratory in nature.
- AEs and SAEs will be analysed as per section 7
- Overall Survival - Measured from the date of registration, an event here is defined as death. Patients are followed up until they have either died or are censored at date last seen. A Kaplan-Meier plot will be produced for each comparison, estimates of median survival will be reported along with associated confidence intervals (where they can be estimated)

8.3 Subgroup Analysis

Exploratory subgroup analyses will be conducted to attempt to ascertain the effect of disease severity on outcomes. The subgroups of 'non-severe disease' and 'severe disease' are defined as those that have a baseline WHO score of < 6 and ≥ 6 respectively. Other exploratory subgroup analyses may be conducted based on known prognostic indicators e.g. age group.

9 SAMPLE SIZE

The tables below demonstrate the operating characteristics of a trial design with the chosen decision criteria, based on a simpler analysis of area under the curve for sequential CRP data, with effect sizes informed from a dataset from 1026 hospitalised COVID-19 patients at Queen Elizabeth Hospital, Birmingham.

It is anticipated that our proposed hierarchical analysis will have superior operating characteristics. In our simulations, we compared a traditional fixed trial design recruiting 120 patients with candidate adaptive designs. We present basic operating characteristics for the fixed design (Table 1) and the chosen adaptive design (Table 2). We studied six scenarios of treatment effect, and estimated, through simulation, the probability of a trial stopping early for "success" or "futility," and ultimately concluding success. Scenarios A, B, and C are beneficial effects of the intervention with (true) treatment effects of 0.25, 0.5 and 0.75 standard deviations, "null" is zero treatment effect and D and E are harmful effects of 0.25 and 0.5 standard deviations. "success" and "futility" are defined as above.

Table 1: Operating characteristics for a fixed trial design of 120 patients

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0	0	0.101	120
A	0	0	0.537	120
B	0	0	0.926	120
C	0	0	0.997	120
D	0	0	0.008	120
E	0	0	0	120

The adaptive design achieves similar probabilities of success in scenarios where the treatment effect is truly beneficial (A, B and C), and increases the probability of success only slightly if the intervention is harmful (D and E). There is some increase in the probability of success if the treatment effect is zero (Type I error) but this is offset by the very substantial reductions in the numbers of patients needed in all scenarios. Moreover, Type I error is not seen as a serious problem as all interventions would be evaluated further in Phase 3 trials.

Table 2: operating characteristics for an adaptive design with interim analyses at 40 and 80 patients

Scenario	Probability stopping early for success	Probability stopping early for futility	Overall probability of success	Mean number of patients
Null	0.140	0.607	0.143	70
A	0.471	0.254	0.573	74
B	0.847	0.062	0.910	61
C	0.974	0.010	0.989	51
D	0.030	0.918	0.031	54
E	0.003	0.985	0.003	47

10 STATISTICAL SOFTWARE

Statistical analyses will be carried out using relevant statistical software; SAS , Stata or R respectively. Version numbers and session details will be stated and logged with any analysis.

11 STORAGE AND ARCHIVING

Catalyst files are stored in a restricted access directory on a secure server and will be saved for archive purposes according to CRCTU policy and procedure.