

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

Benjamin A. Fisher, MD(Res)^{1,2,3*}, Prof Tonny Veenith, PhD^{4,5*}, Daniel Slade, MSc^{3*}, Charlotte Gaskell, MSc³, Matthew Rowland, DPhil⁶, Prof Tony Whitehouse, MD^{4,5}, James Scriven, PhD^{7,8}, Dhruv Parekh, PhD^{4,5,9} Madhu S. Balasubramaniam, MBBS¹⁰, Prof Graham Cooke, DPhil¹¹, Nick Morley, MBBS¹², Zoe Gabriel, MBBS¹³, Matthew P. Wise, DPhil¹⁴, Prof Joanna Porter, PhD¹⁵, Prof Helen McShane, PhD¹⁶, Prof Ling-Pei Ho, DPhil^{17,18}, Prof Philip N. Newsome, PhD^{2,19}, Anna Rowe, PhD^{2,3}, Rowena Sharpe, PhD³, Prof David R. Thickett, DM^{5,9}, Prof Julian Bion, MD^{4,5}, Prof Simon Gates, PhD³, Prof Duncan Richards, DM²⁰ and Prof Pamela Kearns, PhD^{2,3} on behalf of CATALYST investigators[&]

* These authors have made an equal contribution.

[&] Additional investigators of the CATALYST Trial are listed in Supplemental Appendix.

Corresponding authors contact details:

Dr Benjamin A. Fisher, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. Email: b.fisher@bham.ac.uk

Prof. Tonny Veenith, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. Email: t.v.veenith@bham.ac.uk

1. Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, UK

2. National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

3. Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

4. Department of Critical Care Medicine, University Hospitals Birmingham NHS Trust, United Kingdom

5. Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, UK

6. Kadoorie Centre for Critical Care Research, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

7. Department of Infectious Diseases, University Hospitals Birmingham NHS Trust, UK

8. Institute of Microbiology and Infection, University of Birmingham, UK.

9. Department of Respiratory Medicine, University Hospitals Birmingham NHS Trust, UK

10. Department of Critical Care Medicine, Royal Bolton Hospital, Bolton, UK

11. Department of Infectious Disease, Imperial College London, London, UK

- 37 12. Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK
- 38 13. Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
- 39 14. Department of Critical Care Medicine, University Hospital of Wales, Cardiff, UK
- 40 15. Department of Respiratory Medicine, University College Hospital, London, UK
- 41 16. The Jenner Institute, University of Oxford, Oxford, UK
- 42 17. MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, University of Oxford,
43 Oxford, UK
- 44 18. Oxford Interstitial Lung Disease Service, Oxford University Hospitals NHS Foundation Trust,
45 Oxford, UK
- 46 19. Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy,
47 University of Birmingham, Birmingham, UK
- 48 20. Oxford Clinical Trials Research Unit, Botnar Research Centre, University of Oxford, Oxford, UK
- 49

Summary

Background

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

Methods

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

Findings

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

Interpretation

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

Funding

Introduction

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

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

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

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

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

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

Methods

Study design

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

Participants

Eligible patients were 16 years or over, 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), and with a C-Reactive Protein (CRP) ≥ 40 mg/L. The requirement for raised CRP replaced an inclusion criterion for low oxygenation status (oxygen saturation $\leq 94\%$ while breathing ambient air or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen ≤ 300 mmHg) early in the course of recruitment following a change in primary outcome (see below; all protocol changes are summarised in supplementary Table 1). Exclusion criteria are detailed in Supplementary Information.

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

Randomisation

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

Procedures

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

Outcomes

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

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

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

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

Statistical analysis

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

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

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

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

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

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

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

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

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

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

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

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

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

Role of the funding source

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

Results

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

Research in Context

Evidence before this study

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

Added value of this study

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

Implications of all the available evidence

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

Contributors

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

Declaration of interests

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

Data sharing

Participant data and the associated supporting documentation will be available within six months after the publication of this manuscript. Details of our data request process are available on the Cancer Research UK Clinical Trials Unit (CRCTU) website. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The decision to release data will be made by the CRCTU Director's Committee, who will consider the scientific validity of the request, the qualifications and resources of the research group, the views of the Chief Investigator and the Trial Steering Committee, consent arrangements, the practicality of anonymising the requested data and contractual obligations. A data sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship and acknowledgements and obligations for the responsible use of data. An anonymised encrypted dataset will be transferred directly using a secure method and in accordance with the University of Birmingham's IT guidance on encryption of datasets.

Acknowledgements

This trial is supported by the Medical Research Council (MRC) grant number MC_PC_20007. SG is supported by a Senior Investigator Award from the National Institute of Health Research. Staff at the CRCTU are supported by core funding grants from Cancer Research UK (C22436/A25354), the NIHR Biomedical Research Centre (BRC-1215-20009), The Kennedy Trust for Rheumatology Research as part of the Arthritis – Trials Acceleration Programme (KENN161704), and Innovate UK as part of the Midlands – Wales Advanced Therapy Treatment Centres (104232). This paper presents independent research supported by the NIHR Birmingham Biomedical Research Centres at Birmingham, Oxford, Imperial College London and University College London. GC is supported by a NIHR Research Professorship. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Namilumab was provided free of charge by Izana Bioscience, Oxford, UK (now part of Roivant). Infliximab is being provided free of charge by Celltrion.

References

1. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020.
2. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv* 2021: 2021.02.11.21249258.
3. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020; **20**(6): 355-62.
4. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; **383**(2): 120-8.
5. Filbin MR, Mehta A, Schneider AM, et al. Plasma proteomics reveals tissue-specific cell death and mediators of cell-cell interactions in severe COVID-19 patients. *bioRxiv* 2020.
6. Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in Covid-19. *Nature* 2020.
7. Daamen AR, Bachali P, Owen KA, et al. Comprehensive Transcriptomic Analysis of COVID-19 Blood, Lung, and Airway. *bioRxiv* 2020: 2020.05.28.121889.
8. Mann ER, Menon M, Knight SB, et al. Longitudinal immune profiling reveals distinct features of COVID-19 pathogenesis. *medRxiv* 2020: 2020.06.13.20127605.
9. Schulte-Schrepping J, Reusch N, Paclik D, et al. Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment. *Cell* 2020; **182**(6): 1419-40 e23.
10. Hoepel W, Chen H-J, Allahverdiyeva S, et al. Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses. *bioRxiv* 2020: 2020.07.13.190140.
11. Veenith T, Fisher BA, Slade D, et al. CATALYST trial protocol: A multicentre, open-label, phase II, multi-arm trial for an early and accelerated evaluation of the potential treatments for COVID-19 in hospitalised adults. *medRxiv* 2021: 2021.02.10.21251478.
12. Thwaites RS, Sanchez Sevilla Uruchurtu A, Siggins MK, et al. Inflammatory profiles across the spectrum of disease reveal a distinct role for GM-CSF in severe COVID-19. *Science Immunology* 2021; **6**(57): eabg9873.

13. Zhao Y, Kilian C, Turner JE, et al. Clonal expansion and activation of tissue-resident memory-like Th17 cells expressing GM-CSF in the lungs of severe COVID-19 patients. *Sci Immunol* 2021; **6**(56).
14. Williams MA, White SA, Miller JJ, et al. Granulocyte-macrophage colony-stimulating factor induces activation and restores respiratory burst activity in monocytes from septic patients. *J Infect Dis* 1998; **177**(1): 107-15.
15. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe* 2016; **19**(2): 181-93.
16. Hussell T, Pennycook A, Openshaw PJ. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. *Eur J Immunol* 2001; **31**(9): 2566-73.
17. Zhang F, Mears JR, Shakib L, et al. IFN- γ and TNF- α drive a CXCL10+ CCL2+ macrophage phenotype expanded in severe COVID-19 and other diseases with tissue inflammation. *bioRxiv* 2020: 2020.08.05.238360.
18. Robinson PC, Liew DFL, Liew JW, et al. The Potential for Repurposing Anti-TNF as a Therapy for the Treatment of COVID-19. *Med (N Y)* 2020; **1**(1): 90-102.
19. Felton T, Pattison N, Fletcher S, Finney S, Walsh T, Dark P. Co-enrolment to UK Critical Care Studies – A 2019 update. *Journal of the Intensive Care Society*; **0**(0): 1751143720971542.
20. Characterisation WHOWGotC, Management of C-i. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020; **20**(8): e192-e7.
21. Gelman A, Hill J, Vehtari A. Regression and Other Stories. Cambridge: Cambridge University Press; 2020.
22. Bürkner P-C. brms: An R Package for Bayesian Multilevel Models Using Stan. 2017 2017; **80**(1): 28.
23. <https://CRAN.R-project.org/package=brms>.
24. Temesgen Z, Assi M, Shweta FNU, et al. GM-CSF Neutralization With Lenzilumab in Severe COVID-19 Pneumonia: A Case-Cohort Study. *Mayo Clin Proc* 2020; **95**(11): 2382-94.
25. De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol* 2020; **2**(8): e465-e73.
26. Patel J, Beishuizen A, Ruiz XB, et al. A Randomized Trial of Otilimab in Severe COVID-19 Pneumonia (OSCAR). *medRxiv* 2021: 2021.04.14.21255475.
27. Temesgen Z, Burger CD, Baker J, et al. LENZILUMAB EFFICACY AND SAFETY IN NEWLY HOSPITALIZED COVID-19 SUBJECTS: RESULTS FROM THE LIVE-AIR PHASE 3 RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL. *medRxiv* 2021: 2021.05.01.21256470.
28. Pupim L, Wang TS, Hudock K, et al. LB0001 MAVRILIMUMAB IMPROVES OUTCOMES IN PHASE 2 TRIAL IN NON-MECHANICALLY-VENTILATED PATIENTS WITH SEVERE COVID-19 PNEUMONIA AND SYSTEMIC HYPERINFLAMMATION. *Annals of the Rheumatic Diseases* 2021; **80**(Suppl 1): 198-9.
29. Cremer PC, Abbate A, Hudock K, et al. Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol* 2021; **3**(6): e410-e8.
30. Group WHOREAfC-TW, Shankar-Hari M, Vale CL, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA* 2021.
31. Stallmach A, Kortgen A, Gonnert F, Coldewey SM, Reuken P, Bauer M. Infliximab against severe COVID-19-induced cytokine storm syndrome with organ failure-a cautionary case series. *Crit Care* 2020; **24**(1): 444.
32. Notley CA, Inglis JJ, Alzabin S, McCann FE, McNamee KE, Williams RO. Blockade of tumor necrosis factor in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells. *J Exp Med* 2008; **205**(11): 2491-7.

33. Masso-Silva JA, Moshensky A, Lam MTY, et al. Increased peripheral blood neutrophil activation phenotypes and NETosis in critically ill COVID-19 patients: a case series and review of the literature. *Clin Infect Dis* 2021.
34. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. *New England Journal of Medicine* 2020; **384**(6): 497-511.
35. Piccoli L, Campo I, Fregni CS, et al. Neutralization and clearance of GM-CSF by autoantibodies in pulmonary alveolar proteinosis. *Nat Commun* 2015; **6**: 7375.
36. Mehta P, Porter JC, Manson JJ, et al. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. *Lancet Respir Med* 2020; **8**(8): 822-30.

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 (0.0)	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)

¹Vulnerable, mildly frail, moderately frail, severely frail. ²Time from date of hospital admission to date of randomisation.

³The number of patients that have at least one of the following lung disease co-morbidities (chronic obstructive pulmonary disease, asthma, interstitial lung disease).

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

NR, not recordable.

Table 3. Hospital discharge status at day 28. Data was available on all patients (modified intention to 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)

Figure Legends

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

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

Figure 3. WHO clinical progression score over 28 days for usual care versus namilumab. 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.