EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

A Randomised trial of anti–GM-CSF Otilimab in severe COVID-19 pneumonia (OSCAR)

Jatin Patel, Damon Bass, Albertus Beishuizen, Xavier Bocca Ruiz, Hatem Boughanmi, Anthony Cahn, Hugo Colombo, Gerard J. Criner, Katherine Davy, Javier de-Miguel-Díez, Pablo A. Doreski, Sofia Fernandes, Bruno François, Anubha Gupta, Kate Hanrott, Timothy Hatlen, Dave Inman, John D. Isaacs, Emily Jarvis, Natalia Kostina, Tatiana Kropotina, Jean-Claude Lacherade, Divya Lakshminarayanan, Pedro Martinez-Ayala, Charlene McEvoy, Ferhat Meziani, Mehran Monchi, Sumanta Mukherjee, Rosana Muñoz-Bermúdez, Jessica Neisen, Ciara O'Shea, Gaëtan Plantefeve, Lorrie Schifano, Lee E. Schwab, Zainab Shahid, Michinori Shirano, Julia E. Smith, Eduardo Sprinz, Charlotte Summers, Nicolas Terzi, Mark A. Tidswell, Yuliya Trefilova, Russell Williamson, Duncan Wyncoll, Mark Layton

Please cite this article as: Patel J, Bass D, Beishuizen A, *et al*. A Randomised trial of anti–GM-CSF Otilimab in severe COVID-19 pneumonia (OSCAR). *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.01870-2021).

A Randomised Trial of Anti–GM-CSF Otilimab in Severe COVID-19 Pneumonia (OSCAR)

Jatin Patel, MB ChB,[1]* Damon Bass, DO,[2] Albertus Beishuizen, PhD,[3] Xavier Bocca Ruiz, MD,[4] Hatem Boughanmi, MD,[5] Anthony Cahn, MBBS, PhD,[1] Hugo Colombo, MD,[6] Gerard J Criner, MD,[7] Katherine Davy, MSc,[1] Javier de-Miguel-Díez, MD, PhD,[8] Pablo A Doreski, MD,[9] Sofia Fernandes, MD,[1] Bruno François, MD,[10] Anubha Gupta, PhD,[1] Kate Hanrott, PhD,[1] Timothy Hatlen, MD,[11] Dave Inman, MSc,[1] John D Isaacs, MBBS,[12] Emily Jarvis, MSc,[1] Natalia Kostina, MD,[13] Tatiana Kropotina, MD,[14] Jean-Claude Lacherade, MD,[15] Divya Lakshminarayanan, PhD,[16] Pedro Martinez-Ayala, MD,[17] Charlene McEvoy, MD, MPH,[18] Ferhat Meziani, MD, PhD,[19] Mehran Monchi, MD,[20] Sumanta Mukherjee, PhD,[16] Rosana Muñoz-Bermúdez, MD, PhD,[21] Jessica Neisen, PhD,[1]* Ciara O'Shea, PhD, MSc,[22] Gaëtan Plantefeve, MD,[23] Lorrie Schifano, PharmD,[2] Lee E Schwab, MD,[24] Zainab Shahid, MD,[25] Michinori Shirano, MD, PhD,[26] Julia E. Smith, PhD,[1] Eduardo Sprinz, MD, ScD,[27] Charlotte Summers, BM, PhD,[28] Nicolas Terzi, MD, PhD,[29] Mark A Tidswell, MD,[30] Yuliya Trefilova, MD, PhD[31] Russell Williamson, PhD, FRSB,[1]* Duncan Wyncoll, MBBS, FICM,[32] and Mark Layton, MD[1]

[1]GSK Medicines Research Centre, Stevenage, UK; [2]GlaxoSmithKline, Research Triangle Park, NC, USA; [3]Intensive Care Center, Medisch Spectrum Twente, Enschede, Netherlands; [4]Servicio de Neumonologia, Clinica Monte Grande, Buenos Aires, Argentina; [5]Service de Réanimation, CH Valenciennes - Hôpital Jean Bernard, Valenciennes Cedex, France; [6]Clinica Privada Colombo, Córdoba, Argentina; [7]Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine, Temple University Hospital, Philadelphia, PA, USA; [8]Respiratory Department, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain; [9]Clinica Independencia de Munro, Buenos Aires, Argentina; [10]Service Réanimation Polyvalente and Inserm CIC1435 & UMR1092, CHU Limoges, Limoges Cedex, France; [11]Harbor-UCLA Medical Center, Torrance, CA, USA; [12]Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [13]Voronezh Regional Clinical Hospital, Voronezh, Russia; [14]BUZ

Regional Clinical Hospital, Omsk, Russia; [15]Service de Médecine Intensive Réanimation, CHD Vendée - Site De La Roche-sur-Yon, La Roche-Sur-Yon, France; [16]GlaxoSmithKline, Collegeville, PA, USA; [17]Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico; [18]Regions Hospital, St. Paul; Methodist Hospital, St. Louis Park; HealthPartners Institute, Bloomington, MN, USA; [19]Department of Intensive Care (Service de Médecine Intensive - Réanimation), Nouvel Hôpital Civil, Hôpital Universitaire de Strasbourg, Strasbourg, France; CRICS-TRIGGERSEP F-CRIN network, Strasbourg, France; [20]Groupe Hospitalier Sud Ile-de-France, Melun, France; [21]Hospital del Mar-IMIM, Barcelona, Spain; [22]GSK, Dublin, Ireland; [23]Service de Réanimation Polyvalente, CH Victor Dupouy, Argenteuil, France; [24]Holy Cross Health, Silver Spring, MD, USA; [25]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [26]Osaka City General Hospital, Osaka, Japan; [27]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [28]Department of Medicine, University of Cambridge School of Clinical Medicine, Cambridge, UK; [29]Médecine Intensive Réanimation, CHU Grenoble-Alpes; Université Grenoble-Alpes; INSERM U1042, Grenoble, France; [30]Pulmonary and Critical Care, Baystate Medical Centre, Springfield, MA, USA; [31]Perm Regional Clinical Hospital, Perm, Russia; [32]Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, UK.

*At the time the study was conducted.

Corresponding author:

Name: Anthony Cahn

Address: GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY

Tel: +44 1438 766374

Email: tony.x.cahn@gsk.com

Author contributions:

GSK authors contributed to the conception, design, and analysis of data. Study investigators contributed to the acquisition of data. All authors contributed to data interpretation, drafting, or critically revising the article. All authors provided final approval and agreement of accountability.

Funding sources and role: This study (GSK ID: 214094; NCT04376684) was funded by GSK. In 2013, GSK assumed exclusive worldwide responsibility of otilimab (previously MOR103) from MorphoSys AG for all development and commercialisation activities in all therapeutic fields. The study was supported in the United Kingdom by the National Institute for Health Research (NIHR) Comprehensive Research Network (CRN) under the Urgent Public Health clinical trial scheme and the NIHR Newcastle Biomedical Research Centre in Ageing and Long-term Conditions. The views expressed are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care.

Keywords: COVID-19, pneumonia, otilimab, GM-CSF, elderly, clinical trial

Running title: Otilimab in severe COVID-19

Target journal: European Respiratory Journal

Word count: 3311/3000 words
No. tables/figures: 7/8
Supplementary material: investigator and site list, supplementary methods, 6 figures/tables, protocol, and statistical analysis plan for each study part
No. references: 38/40
Abstract: 250/250 words

Plain-language summary

Therapeutic blocking of GM-CSF with otilimab did not significantly improve clinical status in patients with severe COVID-19; however, otilimab demonstrated an acceptable safety profile and reduced markers of inflammation.

Abstract

BACKGROUND

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and dysregulated myeloid cell responses are implicated in the pathophysiology and severity of coronavirus disease 2019 (COVID-19).

METHODS

In this randomised, sequential, multicentre, placebo-controlled, double-blind study, adults aged 18–79 years (Part 1) or ≥70 years (Part 2) with severe COVID-19, respiratory failure, and systemic inflammation (elevated C-reactive protein/ferritin) received a single intravenous infusion of otilimab 90 mg (human anti–GM-CSF monoclonal antibody) plus standard care (NCT04376684). The primary outcome was the proportion of patients alive and free of respiratory failure at Day 28.

RESULTS

In Part 1 (N=806 randomised 1:1 otilimab:placebo), 71% of otilimab-treated patients were alive and free of respiratory failure at Day 28 versus 67% who received placebo; the model-adjusted difference of 5.3% was not statistically significant (95% CI –0.8, 11.4; *P*=0.09). A nominally significant model-adjusted difference of 19.1% (95% CI 5.2, 33.1; *P*=0.009) was observed in the predefined 70–79 years subgroup, but this was not confirmed in Part 2 (N=350 randomised) where the model-adjusted difference was 0.9% (95% CI –9.3, 11.2; *P*=0.86). Compared with placebo, otilimab resulted in lower serum concentrations of key inflammatory markers, including the putative pharmacodynamic biomarker CCL17, indicative of GM-CSF pathway blockade. Adverse events were comparable between groups and consistent with severe COVID-19.

CONCLUSIONS

There was no significant difference in the proportion of patients alive and free of respiratory failure at Day 28. However, despite the lack of clinical benefit, a reduction in inflammatory markers was observed with otilimab, in addition to an acceptable safety profile.

Introduction

Severe COVID-19 is characterised by respiratory and/or multiorgan failure [1]. A subset of patients displays systemic hyperinflammation including dysregulated myeloid cell responses [2-4]. Older age and associated immunosenescence and underlying comorbidities may predispose patients to similar immune abnormalities to those observed in COVID-19 [5, 6], increasing their risk of severe disease and mortality [7-9].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is implicated in driving hyperinflammation in severe COVID-19 [10-14], with increased circulating concentrations reportedly associated with COVID-19 severity and mortality [12, 15]. This may be due to the putative role of GM-CSF in myeloid cell activation, differentiation, survival, and priming to enhance inflammatory cytokine and chemokine production, leading to further myeloid cell recruitment to sites of inflammation. This potentially produces a positive feedback loop driving cytokine and chemokine production, hyperinflammation, and tissue damage [10, 11].

Otilimab is a high-affinity, fully human, anti–GM-CSF monoclonal antibody (IgG1λ) that reduces inflammatory activity in rheumatoid arthritis (RA) [16].
GM-CSF inhibition with otilimab was hypothesised to reduce the production of proinflammatory cytokines and chemokines, decrease myeloid cell migration, and modulate hyperinflammation, leading to an improved outcome in severe COVID-19 [10]. The otilimab in severe COVID-19–related disease (OSCAR) trial was designed to investigate the efficacy and safety of otilimab in patients with acute respiratory failure and systemic inflammation due to severe COVID-19.

Methods

Study design

OSCAR was a randomised, multicentre, placebo-controlled, double-blind study (214094; NCT04376684) conducted at 121 sites across 19 countries (**Supplementary Materials**). This sequential study was conducted in 2 parts: Part 1 enrolled patients aged 18 to ≤79 years between 28 May 2020 and 15 November 2020, with the last patient completing Day 60 on 13 January 2021. Part 1 results

indicated a potential benefit of otilimab in a predefined subgroup of patients aged 70–79 years. Therefore, the original protocol was amended to include Part 2, which enrolled only patients aged ≥70 years between 15 February 2021 and 19 June 2021, with the last patient completing Day 60 on 16 August 2021.

Patients were randomised 1:1 in a blinded manner, using interactive response technology (block size of 4) to receive otilimab or matched placebo. Patients were monitored daily until Day 28 (or until hospital discharge), with follow-up assessments at Days 42 and 60.

The study was conducted in accordance with the Declaration of Helsinki, Council for International Organisations of Medical Sciences International Ethical Guidelines, International Conference on Harmonisation, Good Clinical Practice, and applicable country-specific regulatory requirements. The protocol was approved by relevant institutional review boards. Before enrolment, informed consent was obtained from the patient or their legally authorised representative. An independent data monitoring committee monitored in-stream unblinded safety and efficacy data throughout the study.

Patients

Eligible patients were aged 18 to 79 years in Part 1 and ≥70 years in Part 2, had a positive SARS-CoV-2 result from any validated test (predominantly reverse transcription-polymerase chain reaction), and were hospitalised due to radiographically confirmed pneumonia consistent with COVID-19. All patients had a clinical status of Category 5 or 6 in the modified World Health Organisation (WHO) Ordinal Scale for Clinical Improvement [17] **(Supplementary Methods)**, defined by recent onset of oxygenation impairment requiring either high-flow oxygen (≥15 L/min; Category 5), non-invasive ventilation (NIV; Category 5), or invasive mechanical ventilation (IMV) without additional organ support (Category 6) ≤48 hours prior to dosing. Serum concentrations of inflammatory markers, C-reactive protein (CRP) or ferritin, were required to be above the upper limit of normal.

Patients were excluded if death was predicted within 48 hours; they had multiple organ failure according to the investigator's opinion and/or a Sequential Organ Failure Assessment (SOFA) [18] score >10; or were receiving extracorporeal

membrane oxygenation, haemofiltration/dialysis, or >1 inotrope/vasopressor of any class. Patients who had received intravenous (IV) immunoglobulin, monoclonal antibody, or immunosuppressant therapy within the past 3 months or currently receiving chronic oral corticosteroids (>10 mg/day prednisone or equivalent) for a non–COVID-19 indication were also excluded. Full eligibility criteria are provided in the protocol (**Supplementary Materials**).

Study treatments

Patients received either a single 1-hour IV infusion of otilimab 90 mg or placebo on Day 1 and standard of care (SoC) according to current clinical guidelines and institutional protocols. This otilimab dosing regimen was predicted to result in serum concentrations remaining within the target range for ~1 week, which was deemed to be sufficient to inhibit the expected levels of GM-CSF in circulation/tissue and induce an anti-inflammatory effect, while allowing the return to normal GM-CSF levels in the recovery phase, during which GM-CSF expression may promote lung repair [10].

Endpoints and assessments

The primary endpoint was the proportion of patients alive and free of respiratory failure (clinical status: Categories 1–4) at Day 28. Key secondary endpoints included all-cause mortality at Days 28 (post hoc for Part 1) and 60; time to all-cause mortality up to Day 60; participants alive and free of respiratory failure at Day 7, 14, 42, and 60; time to recovery from respiratory failure at Day 28; time to last dependence on supplementary oxygen up to Day 28; time to final intensive care unit (ICU) discharge up to Day 28; time to first discharge from investigator site up to Day 60 (revised before unblinding in Part 1); time to first hospital discharge to non-hospitalised residence up to Day 60 (revised before unblinding in Part 1); and adverse events (AEs) and serious AEs (SAEs) up to Day 60. Exploratory endpoints are provided in the **Supplementary Materials**.

Biomarker and pharmacokinetic (PK) assessments

Blood samples for otilimab and GM-CSF–otilimab complex concentrations were collected on Days 1, 2, 7, and 14. Further details of PK and exposure-response analyses are provided in the **Supplementary Materials**.

Free GM-CSF was assessed using an ultrasensitive immunoassay based on single molecule array (Simoa™) technology. Target engagement was estimated from the target-mediated drug disposition model [19] developed using concentrations of free GM-CSF at baseline, otilimab, and GM-CSF–otilimab complex over time.

Blood samples were collected at screening and on Days 2 (Part 1 only), 4, and 7 for measurement of serum concentrations of inflammatory markers, using ECL-based immunoassays and neutrophil-to-lymphocyte ratios (NLRs) derived from clinical haematology panels.

Statistical analysis

Parts 1 and 2 were analysed separately. Full details are provided in the statistical analysis plan (SAP) (**Supplementary Materials**). Part 1 used a group sequential design to control for multiplicity, with interim analyses for futility and efficacy. In Part 1 and Part 2, a sample size of 800 and 346 patients provided approximately 90% and 80% power to detect a difference of 12% and 15%, respectively, in the proportion of patients alive and free of respiratory failure at a one-sided 2.5% significance level and an assumed placebo response rate of 45%.

The primary endpoint was assessed using logistic regression, adjusting for treatment, sex (Part 2 only), age, and clinical status at baseline. Missing data in the overall primary analysis were imputed using multiple imputation, assuming data were missing at random and adjusting for analysis covariates. The primary endpoint was also analysed in predefined stratification factors based on clinical status, age (post hoc in Part 2), clinical status by age (Part 1 only), and sex (Part 2 only), as described in the SAP (**Supplementary Materials)**.

Given that OSCAR was a single-dose trial, and dosing was anticipated to occur very quickly following randomisation, it was assumed that any patients who were randomised but did not receive treatment were those who withdrew consent or were randomised in error. As these patients would have no post-baseline data, the population for primary analyses included all patients who were randomised and received study drug (modified intent-to-treat [mITT]). The SAP was finalised before

the clinical database was locked. For ease of interpretation, two-sided *P*-values with 5% significance level are presented.

Results

Baseline population findings

In Part 1, 793 patients were included in the mITT population (otilimab n=395; placebo n=398), with patients aged 70–79 years accounting for 23% of the overall population; in Part 2, 347 patients were included in the mITT population (otilimab n=174; placebo n=173) **(Figure 1)**. In both parts, baseline demographics and disease characteristics were generally well balanced between groups and were reflective of severe COVID-19 **(Table 1)**. Compared with Part 1, a larger proportion of patients in Part 2 were in Category 5.

Primary endpoint: patients alive and free of respiratory failure

In Part 1, 71% of patients in the otilimab group were alive and free of respiratory failure at Day 28 versus 67% who received placebo; the model-adjusted difference of 5.3% was not statistically significant (95% CI –0.8, 11.4; *P*=0.09) **(Figure 2A).** Model-adjusted differences for patients in Categories 5 and 6 were 5.9% (95% CI –0.8, 12.7) and 4.6% (95% CI –9.6, 18.8), respectively **(Figure 2A).** In the predefined subgroup of patients aged 70–79 years, the model-adjusted difference was 19.1% (95% CI 5.2, 33.1; nominal *P*=0.009); this response was consistent regardless of clinical status **(Figure 2A).**

In Part 2, 52% of patients who received otilimab were alive and free of respiratory failure at Day 28 versus 51% who received placebo (model-adjusted difference: 0.9% [95% CI –9.3, 11.2; *P*=0.86]) **(Figure 2B).** For patients in Category 5 and 6, the model-adjusted difference was 4.2% (95% CI –6.9, 15.4) and –17.5% (95% CI –42.7, 7.6), respectively **(Figure 2B).** Model-adjusted differences were –2.1% (95% CI –14.0, 9.8; *P*=0.73) in patients aged 70–<80 and 7.7% (95% CI –14.7, 30.2; *P*=0.51) in patients aged ≥80 years **(Figure 2B).** Post hoc analyses of the primary endpoint by baseline characteristic are presented in **Supplementary Figure S1**.

Secondary endpoint: all-cause mortality

In Part 1, all-cause mortality at Day 60 was 23% in the otilimab group compared with 24% receiving placebo (model-adjusted difference –2.4% [95% CI –8.0, 3.3]; *P*=0.41) **(Figure 3A).** In the 70–79 years subgroup, there was lower mortality at Day 60 with otilimab (27%) versus placebo (41%) (model-adjusted difference –14.4% [95% CI –27.9, –0.9]; nominal *P*=0.04).

In Part 2, all-cause mortality at Day 28 was 37% in the otilimab group compared with 41% in the placebo group (model-adjusted difference –5.2 [95% CI –15.1, 4.7]; *P*=0.31) **(Figure 3B).** Mortality at Day 60 was 43% in the otilimab group and 45% in the placebo group, with a model-adjusted difference of –2.2% (95% CI –12.4, 7.9; *P*=0.67). No significant differences in mortality at Days 28 or 60 were observed in the predefined subgroups of either part.

Additional secondary and exploratory efficacy endpoints

Generally, there were no significant differences in time-to-event analyses in the Part 1 mITT population between treatment groups **(Figure 4A, 5A, Supplementary Figure S2A–G).** However, improvements with otilimab versus placebo were observed in the 70–79 years subgroup **(Figure 4B, 5B, Supplementary Figure S2A–D)**, with treatment effects apparent 7–10 days post-infusion.

There was a short-term, numerical benefit of otilimab versus placebo in most time-to-event analyses in Part 2, including time to recovery from respiratory failure, as well as an early delay in time to IMV; separation between groups was observed from around Day 3 and converged around Day 10 **(Figure 4C, Supplementary Figure S2A, B, E, G)**. There was no difference between otilimab and placebo in time to all-cause mortality up to Day 60 **(Figure 5C).**

In the exploratory endpoint of change from baseline in FiO_2, a greater reduction was observed in patients receiving otilimab versus placebo in the Part 1 mITT population, Part 1 70–79 years subgroup, and Part 2 mITT population up to Day 14 **(Supplementary Figure S2H)**.

Safety endpoints

In both parts, no safety signals related to otilimab were identified. Overall safety findings, including the scope of AEs and SAEs, were reflective of the severe COVID-19 population, and no clinically meaningful differences in AEs, including the rates of secondary infections, were observed **(Table 2)**.

Biomarkers

Similar free GM-CSF concentrations were observed in both parts at baseline and Day 1 **(Table 1 and Supplementary Table S1)**. In Part 1, free GM-CSF levels in the otilimab arm at Day 2, proximal to C_{max}, were reduced by at least 95% to a mean of 0.037 ng/L with 255/381 samples (67%) falling below the assay lower limit of quantification (0.036 ng/L); levels in the placebo arm remained unchanged. Day 2 data were not collected in Part 2, and post-Day 2 data are not available.

Otilimab also induced rapid reductions in other key inflammatory markers compared with placebo in the 7 days after infusion **(Supplementary Figure S3).** Data from the aged 70–79 years subgroup of Part 1 were similar to the total Part 1 population. In both parts, greater reductions in interleukin (IL)-6 and IL-10 were observed with otilimab versus placebo at Day 2 and/or 4, converging by Day 7. CRP concentrations decreased from baseline in both groups, although Part 2 showed greater reductions with otilimab by Day 7. CC chemokine ligand (CCL)17 concentrations increased in the placebo group, but not in the otilimab group in both parts, and a greater reduction from baseline in NLR was observed with otilimab at Days 4 and 7 in Part 2; however, the effect with placebo varied between study parts, as did the patterns observed for macrophage chemotactic protein-1 (MCP-1) and IL-8.

PK

Similar serum concentrations of otilimab **(Supplementary Figure S4 and Table S1)** and GM-CSF–otilimab complex concentrations **(Supplementary Figure S5 and Table S1)** were observed in both parts. The target engagement model predicted 91%, 74%, and 23% target engagement at Day 2, 4, and 7, respectively.

Across all patients in both parts, the PK model-derived mean otilimab exposure parameters, maximum concentration (C_{max}) and area under the concentration-time

curve (AUC), following a single dose of 90 mg, were 18.9 µg/mL and 50.7 µg*days/mL, respectively. The population clearance rate of otilimab was 1.67 L/day, and effective half-life was 3.65 days.

Clinical response (patients alive and free of respiratory failure on Day 28, all-cause mortality at Day 60, and improvements in clinical status over time) when stratified by placebo and quartile of otilimab exposure (AUC or C_{max}) suggested that a higher otilimab exposure was associated with better response **(Supplementary Figure S6)**; however, patients in the lowest quartile group had a worse response than those in the placebo group. Day 7 and 14 data for the proportion of patients alive and free of respiratory failure were similar to Day 28 data. There was no clear relationship between exposure and serious infection or change in CRP, IL-6, CCL17, or MCP-1.

Discussion

In this large study of hospitalised adults with COVID-19 aged 18–79 (Part 1) and ≥70 years (Part 2), administration of otilimab was not associated with a significant difference in the proportion of patients alive and free of respiratory failure at Day 28.

In Part 1, otilimab was associated with a nonsignificant increase in the proportion of patients alive and free of respiratory failure at Day 28. However, significantly more patients in a predefined subgroup aged 70–79 years receiving otilimab met this endpoint compared with those receiving placebo. There was also a corresponding decrease in all-cause mortality at Day 60. Immunosenescence and “inflammaging”, associated with normal aging of the immune system, may predispose older patients with COVID-19 to inappropriate, myeloid cell-driven hyperinflammation [5, 6]. Further evidence emerged at the time of Part 1 analysis supporting the potential role of GM-CSF and myeloid cells in COVID-19 pathogenesis [10-13].

Based on Part 1 findings and the high mortality rate observed in elderly patients with severe COVID-19 [9], Part 2 specifically evaluated the potential clinical benefit in patients aged ≥70 years. This extension of the study did not, however, confirm the significant difference between otilimab and placebo for the primary endpoint observed in Part 1. Despite a credible hypothesis, it is likely that observations in a

single subgroup in Part 1 were due to chance. Other confounding factors may have also contributed to the differences in results, including slight variations in patient demographics, risk profiles, and clinical status between parts, in addition to variability in mortality rates across geographies [20], improvements in SoC and patient management, and the changing prevalence and virulence of viral variants at the different stages of the pandemic. Additional study limitations include the use of an estimated birth date (with only the year of birth recorded) to determine patient age and low patient numbers in certain subgroups, which made it difficult to perform some sub-analyses.

Low systemic target engagement levels after Day 4 may have impacted efficacy. However, patients with the lowest otilimab exposure generally had a worse clinical response than placebo-treated patients. This suggests a potential bidirectional interaction between PK and response, whereby patients with more severe disease have increased otilimab clearance, causing an apparent exposure-response relationship. Thus, exposure-response data cannot indicate whether a higher dose of otilimab would provide any additional benefit. Furthermore, while a potential early benefit in respiratory status was observed within the first ~10 days of dosing in Part 2, the apparent benefit in the ≥70 years subgroup in Part 1 was only observed after Day 10, despite a decrease in otilimab concentration over Days 1–7, suggesting a delay in treatment effect. Therefore, multiple doses may not have been more effective. However, given that the findings of an overall benefit in most of the time-to-event analyses through to Day 28 in the ≥70 years subgroup of Part 1 are not replicated in Part 2 (except for decreased FiO_2 requirement), despite a similar population, the observed differences between parts during the early stages of the studies are unlikely to be real.

In both parts of OSCAR, otilimab treatment resulted in lower concentrations of the putative pharmacodynamic biomarker for otilimab activity, CCL17 [22] in the 7 days post-infusion with no convergence with placebo, indicating successful target engagement and inhibition of pathways downstream of GM-CSF. Inflammatory markers IL-6 and IL-10 are generally increased in hospitalised patients with COVID-19 and associated with disease severity [23]. In the RECOVERY study, inhibition of IL-6 reduced mortality and improved clinical outcomes [24]. The reduction in these

cytokines observed with otilimab may be associated with the delay in clinical deterioration observed in the first week in Part 2. However, the otilimab group converged with placebo by Day 7, coinciding with the decrease in target engagement from 95% at end of infusion to 23% by Day 7. This could be due to the shorter than previously observed effective half-life of otilimab in patients with COVID-19.

Elevated NLR is a predictor for critical disease [25], and neutrophils have been proposed to have an important role in COVID-19 pneumonia [2, 4, 26]. Otilimab was associated with decreased NLR from baseline up to Day 7 in Part 2, which suggests an early reduction in circulating neutrophil numbers and/or repopulation of lymphocytes and potential dampening of the hyperinflammatory response following GM-CSF inhibition [26, 27]. As all observed biomarker changes were systemic, it is unclear whether these changes were reflected in the lungs, where multiple mechanisms may lead to lung injury.

The lack of a clinically meaningful benefit of otilimab in this severe COVID-19 population may be due to the highly complex and only partially characterised multiplicity of cytokines, chemokines, and cellular components involved in COVID-19 pathophysiology. With new evidence continually emerging, combination therapies, targeting multiple pathways [28, 29], have been adopted into treatment regimens and guidelines [1]. Furthermore, the timing of intervention may be key. OSCAR included patients with already profound respiratory failure and systemic hyperinflammation. However, a window of opportunity may exist in the early stage of hyperinflammation, before progression to significant respiratory failure [11]. This is suggested by the results of the LIVE-AIR study in which anti–GM-CSF lenzilumab was less effective in patients with higher CRP concentrations [30]. Both parts of OSCAR demonstrated the ability of otilimab to decrease FiO_2 more rapidly in all age groups to Day 12–14. This apparent improvement in gaseous exchange in the lungs was not, however, associated with improved clinical outcomes.

Recent *in vitro* studies suggested that binding of the SARS-CoV-2 spike protein to circulating mononuclear cells directly induces GM-CSF secretion, providing further evidence of a role for GM-CSF in the immune response to the virus [31]. However, clinical anti–GM-CSF therapy has generated mixed results in various COVID-19 trials. The anti–GM-CSFRα mavrilimumab demonstrated efficacy in a Phase 2 trial

[32]; however, the Phase 3 trial did not meet the primary endpoint, leading to its discontinuation in COVID-19 [33]. Anti–GM-CSF namilumab demonstrated a reduction in CRP in the CATALYST trial and trends toward clinical improvement, but the study was not powered for these outcomes [34]. Finally, while LIVE-AIR demonstrated that early intervention with lenzilumab decreases CRP and improves the likelihood of survival without ventilation [30, 35], this was not supported by the ACTIV-5/BET-B trial of lenzilumab plus remdesivir, which failed to meet the same primary endpoint of survival without ventilation [36]. Furthermore, lenzilumab did not significantly improve mortality rates in the overall population of either trial [30, 36]. This inconclusive evidence for the benefit of anti–GM-CSF monotherapy in COVID-19 may be linked to the varying disease severity of the patient populations and the different endpoints used in the different studies. Nevertheless, inflammatory biomarker findings in OSCAR continue to support the ongoing evaluation of otilimab in other immune-inflammatory conditions. Indeed, following two Phase 2 studies in RA [16, 22], a large global Phase 3 RA programme is ongoing [37-39].

The AE rate for OSCAR was as expected for a population with severe COVID-19 pneumonia, with the most common SAE being respiratory failure. No clinically meaningful difference was observed between all AEs, including, importantly, the rates of COVID secondary infections, and no safety signals related to otilimab treatment were identified.

Treatment with a single dose of otilimab did not improve the proportion of patients alive and free of respiratory failure at Day 28. Target engagement and a reduction in inflammatory markers were observed, in addition to an acceptable safety profile in a severely ill patient population.

Acknowledgments

We thank all the patients for their participation in this important research. We thank Gift Nyamundanda and Johannes Freudenberg for their work on the biomarker analyses; the global clinical operations delivery managers, Kai Hove and Jack Siderfin; and the global study data managers, Sam Birleson, Laurence Harvey, and Oyiza Momoh. Medical writing support, in the form of editorial checks, figure

development, and assistance with submission, was provided by Leigh O'Connor-Jones, PhD, and Clare Cunningham, PhD, of Fishawack Indicia Ltd. UK, part of Fishawack Health (funded by GSK).

Conflicts of interest

JP, DB, AC, KD, SF, AG, KH, DI, EJ, DL, SM, COS, LS, JES, RW, and ML are shareholders and/or employees of GSK. AB, XBR, HB, HC, GJC, JdMD, PD, BF, TH, JDI, NK, TK, JCL, PMA, CM, FM, MM, RMB, GP, LES, ZS, MS, ES, CS, NT, and YT were investigators in the OSCAR trial, which was funded by GSK. XBR has served as a clinical trial investigator for AstraZeneca and Zambon. MAT and DW received a fee for serving on the IDMC for this study. BF reports consultancy fees with GSK, Enlivex, Inotrem, Takeda, Aridis, Transgene, AM-Pharma, Asahi-Kasai and Biomérieux within the last 36 months. RM-B has participated in an advisory board for GSK. JDI has received research funding from GSK, Janssen, and Pfizer, and personal fees from AbbVie, BMS, Gilead, Roche, and UCB, all outside the submitted work, as well as support for event attendance from Eli Lilly and Gilead. AB has received consultancy fees from GSK. CM has received research funding from the National Institutes of Health, US Department of Defense, Patient-Centered Outcomes Research Institute, GSK, and AstraZeneca. CS' institution has received research funding from GSK, AstraZeneca, the Wellcome Trust, The Medical Research Council, and National Institute for Health Research to support her work outside the area of the submitted manuscript. CS has received personal fees from AbbVie, Roche, and GSK. GJC has received research grants from ALung Technologies Inc, American College of Radiology, American Lung Associations, AstraZeneca, BioScale Inc., Boehringer Ingelheim, BREATH Therapeutics Inc, COPD Foundation, Coridea/ZIDAN, Corvus, Dr Karen Burns of St Michael's Hospital, Fisher & Paykel Healthcare Ltd, Galapagos NV, GSK, Kinevent, Lungpacer Medical Inc, National Heart Lung & Blood Institute, Nurvaira Inc, Patient-Centered Outcomes Research Institute, Pulmonary Fibrosis Foundation, PulmonX, Respironics Inc, Respivant Sciences, Spiration Inc., Steward St Elizabeth's Medical Center of Boston Inc, and Veracyte Inc; and received personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Broncus Medical, CSA Medical, EOLO Medical, Gala Therapeutics, GSK, Helios Medical, Ion, Merck, Medtronic, Mereo BioPharma,

NGM Biopharmaceuticals, Novartis, Olympus, PulmonX, Respironics Inc, Respivant Sciences, The Implementation Group, and Verona Pharma. JN is an employee and shareholder of AstraZeneca and a shareholder and former employee of GSK. LES reports holding shares in Johnson & Johnson and BMS. ZS has received research funding from Karyopharm. MS is an investigator in separate trials funded by Roche and AstraZeneca. ES participates on a Data Safety Monitoring Board/Advisory Board for, and has received consulting fees and honoraria from, GSK, Janssen, and Gilead. MAT received a fee for serving on the IDMC for this study, as well as for serving on a Data Safety Monitoring Board/Advisory Board for Spectral Diagnostics Inc, ReAlta Life Sciences Inc, Celltrion Inc, AstraZeneca, and Molecular Partners AG. Additionally, MAT has held a research contract with Edesa Biotech Research Inc, RevImmune SAS, Spectral Diagnostics, Beyond Air Inc, NIH, and NHLBI. DW received a fee for serving on the IDMC for this study, has served as a study adjudicator for AstraZeneca, and reports consulting fees and/or honoraria from Gilead and Shionogi. JdMD, HB, JCL, PMA, TH, GP, NT, MS, NK, TK, YT, and MM have no other conflicts of interest to declare.

Data sharing statement

GSK makes available anonymised individual participant data and associated documents from interventional clinical studies, which evaluate medicines upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access original data for studies that have been re-analysed, other types of GSK sponsored research, study documents without patient-level data, and clinical studies not listed, please submit an enquiry via the website.

Tables

Table 1. Baseline characteristics

	Part 1				Part 2	
	Overall population		Age 70–79 years[1]		Overall population	
Characteristic	**Otilimab (N=403)**	**Placebo (N=403)**	**Otilimab (n=88)**	**Placebo (n=92)**	**Otilimab (N=175)**	**Placebo (N=175)**
Male sex – n (%)	302 (75)	275 (68)	65 (74)	57 (62)	102 (58)	100 (57)
Age – mean (SD)	59.8 (11.7)	59.4 (11.9)	74.0 (2.8)	74.0 (2.8)	75.3 (4.7)	75.0 (4.7)
Age group – n (%)						
Part 1:						
<60 years	178 (44)	185 (46)	0	0	–	–
60–69 years	135 (33)	127 (32)	0	0	–	–
70–79 years	90 (22)	91 (23)	88 (100)	92 (100)	–	–
Part 2:						
<70 years[2]	–	–	–	–	9 (5)	5 (3)
70–79 years	–	–	–	–	126 (72)	136 (78)
≥80 years	–	–	–	–	40 (23)	34 (19)
Weight (kg) – mean (SD)	88.0 (20.9)	88.2 (20.9)	84.6 (20.2)	80.0 (14.2)	83.9 (16.2)	81.9 (16.5)
Race or ethnic group – n (%)						
American Indian or Alaska Native	30 (8)	24 (6)	3 (3)	4 (4)	8 (5)	3 (2)
Asian	57 (14)	73 (19)	12 (14)	18 (20)	5 (3)	15 (9)
Black or African American	26 (7)	25 (6)	5 (6)	3 (3)	6 (3)	6 (3)
White	272 (69)	262 (67)	67 (77)	64 (71)	155 (89)	150 (86)
Hispanic or Latino	125 (31)	116 (29)	13 (15)	18 (20)	58 (33)	37 (21)
Clinical status – n (%)						
Category 5: Hospitalised, high-flow oxygen, non-invasive ventilation	311 (77)	311 (77)	63 (72)	68 (74)	150 (86)	148 (85)
Category 6: Hospitalised, mechanical ventilation	89 (22)	89 (22)	24 (27)	23 (25)	25 (14)	27 (15)
ICU status – n (%)						
Not in ICU and not on mechanical ventilation	97 (24)	98 (24)	13 (15)	17 (18)	79 (45)	83 (47)
In ICU and not on mechanical ventilation	209 (52)	211 (52)	49 (56)	52 (57)	69 (39)	62 (35)

In ICU and on mechanical ventilation	97 (24)	94 (23)	26 (30)	23 (25)	27 (15)	30 (17)
Biomarkers – mean (SD)[3]						
CRP (mg/L)	111.8 (86.0)	116.3 (84.5)	109.7 (79)	128.8 (82.2)	96.1 (79.4)	93.5 (77.7)
Ferritin (µg/L)	1247.7 (1242.9)	1147.4 (1041.6)	1493.1 (1916)	1248.4 (1201.3)	1482.3 (1697.3)	1177.4 (1060.7)
GM-CSF (ng/L)	0.71 (0.84)	0.72 (0.76)	0.82 (1.19)	0.73 (0.71)	0.82 (1.44)	0.80 (0.95)
Residence prior to hospital admission – n (%)						
Independent or community dwelling	392 (98)	391 (97)	na	na	173 (99)	169 (97)
Long-term care facility	7 (2)	10 (2)	na	na	2 (1)	6 (3)
Current comorbidity[4] – n (%)						
Hypertension	192 (48)	209 (52)	59 (67)	61 (66)	113 (65)	129 (74)
Diabetes	147 (36)	149 (37)	31 (35)	39 (42)	57 (33)	63 (36)
Hyperlipidaemia	97 (24)	96 (24)	35 (40)	41 (45)	45 (26)	53 (30)
Heart disorder	51 (13)	45 (11)	21 (24)	21 (23)	35 (20)	47 (27)
Pretreatment medications[4,5] – n (%)						
Corticosteroids (including dexamethasone)	332 (84)	330 (83)	72 (82)	74 (80)	150 (86)	148 (86)
Dexamethasone	281 (71)	267 (67)	64 (73)	66 (72)	137 (79)	125 (72)
Remdesivir	127 (32)	142 (36)	28 (32)	32 (35)	12 (7)	22 (13)
Convalescent plasma therapy	20 (5)	24 (6)	5 (6)	4 (4)	na	na
Immunosuppressants	0	0	0	0	1 (<1)	0
Anti-IL-6 therapies	0	0	0	0	1 (<1)[6]	0
Antiviral	136 (34)	155 (39)	29 (33)	38 (41)	29 (17)	44 (25)
COVID-19 vaccine	na	na	na	na	2 (4)	1 (2)
Geographic region[4] – n (%)						
USA	98 (24)	90 (22)	20 (23)	23 (25)	1 (<1)	6 (3)
Europe[7]	142 (35)	160 (40)	41 (47)	38 (41)	69 (39)	78 (45)
Latin America[8]	68 (17)	53 (13)	8 (9)	8 (9)	53 (30)	31 (18)
Rest of World[9]	95 (24)	100 (25)	19 (22)	23 (25)	44 (25)	49 (28)

[1]Baseline characteristics in the Part 1 age 70–79 years subgroup are presented in the mITT population.

[2]Patient age was derived from the date of screening visit, year of birth (provided at screening) and an assumed birth date of June 30; therefore, some patients were recorded as <70.

[3]Biomarkers summarised by actual treatment received.

[4]Data in the Part 1 age 70–79 years group are from Day 4.

[5]A dose or infusion of medication used prior to Day 1 (day of dosing of study drug), irrespective of whether medication is continued after dosing.

[6]One patient who had received anti–IL-6 therapy was included in error.

[7]Belgium, France, Italy, Netherlands, Poland, Spain, UK.

[8]Argentina, Brazil, Chile, Colombia, Mexico, Peru.

[9]Canada, India, Japan, Russian Federation, South Africa.

CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICU, intensive care unit; IL, interleukin; mITT, modified intent-to-treat; na, not available; SD, standard deviation.

Table 2. Adverse events

	Part 1				Part 2	
Adverse event	Safety population		Age 70–79 years		Safety population	
	Otilimab (N=397)	Placebo (N=396)	Otilimab (n=89)	Placebo (n=91)	Otilimab (n=174)	Placebo (n=173)
Any adverse event						
Patients with ≥1 event, n (%)	274 (69)	265 (67)	73 (82)	68 (75)	140 (80)	133 (77)
Any serious adverse event						
Patients with ≥1 event, n (%)	124 (31)	147 (37)	33 (37)	49 (54)	90 (52)	90 (52)
Most common adverse events ≥5% in any group, n (%)						
Constipation	39 (10)	35 (9)	16 (18)	14 (15)	16 (9)	15 (9)
Pneumonia	43 (11)	29 (7)	13 (15)	11 (12)	12 (7)	17 (10)
Acute kidney injury	23 (6)	25 (6)	8 (9)	11 (12)	14 (8)	12 (7)
Anaemia	18 (5)	22 (6)	5 (6)	8 (9)	11 (6)	10 (6)
Respiratory failure	19 (5)	21 (5)	6 (7)	9 (10)	7 (4)	8 (5)
Hypotension	14 (4)	16 (4)	1 (1)	6 (7)	10 (6)	13 (8)
Atrial fibrillation	12 (3)	18 (5)	5 (6)	9 (10)	9 (5)	12 (7)
Septic shock	18 (5)	16 (4)	4 (4)	2 (2)	10 (6)	6 (3)
Pulmonary embolism	13 (3)	25 (6)	2 (2)	9 (10)	3 (2)	7 (4)
Hypoxaemia	10 (3)	13 (3)	1 (1)	8 (9)	10 (6)	12 (7)
MODS	12 (3)	16 (4)	3 (3)	5 (5)	6 (3)	11 (6)
Hypokalaemia	15 (4)	16 (4)	7 (8)	6 (7)	8 (5)	4 (2)
Diarrhoea	15 (4)	18 (5)	4 (4)	6 (7)	4 (2)	5 (3)
Urinary tract infection	13 (3)	14 (4)	3 (3)	5 (5)	5 (3)	10 (6)
Pneumothorax	17 (4)	15 (4)	3 (3)	6 (7)	6 (3)	3 (2)
Pyrexia	20 (5)	15 (4)	3 (3)	6 (7)	1 (<1)	4 (2)

Adverse event	Part 1				Part 2	
	Safety population		Age 70–79 years		Safety population	
	Otilimab	Placebo	Otilimab	Placebo	Otilimab	Placebo
Hyperglycaemia	12 (3)	14 (4)	4 (4)	3 (3)	10 (6)	4 (2)
Delirium	17 (4)	17 (4)	4 (4)	5 (5)	3 (2)	2 (1)
Hyperkalaemia	17 (4)	13 (3)	5 (6)	7 (8)	4 (2)	4 (2)
Hypertension	17 (4)	10 (3)	6 (7)	3 (3)	6 (3)	5 (3)
Acute respiratory failure	10 (3)	11 (3)	5 (6)	3 (3)	6 (3)	9 (5)
Hepatocellular injury	6 (2)	5 (1)	5 (6)	1 (1)	14 (9)	10 (6)
Hypernatraemia	20 (5)	10 (3)	2 (2)	6 (7)	3 (2)	1 (<1)
Insomnia	12 (3)	5 (1)	3 (3)	2 (2)	8 (5)	7 (4)
Sepsis	7 (2)	12 (3)	1 (1)	6 (7)	6 (3)	3 (2)
Decubitus ulcer	16 (4)	9 (2)	8 (9)	3 (3)	0	2 (1)
Fluid overload	1 (<1)	2 (<1)	0	1 (1)	9 (5)	5 (3)
Most common serious adverse events ≥5% any group, n (%)						
Respiratory failure	17 (4)	18 (5)	6 (7)	8 (9)	6 (3)	8 (5)
MODS	12 (3)	15 (4)	3 (3)	5 (5)	6 (3)	8 (5)
Septic shock	14 (4)	13 (3)	4 (4)	2 (2)	8 (5)	5 (3)
Acute respiratory failure	9 (2)	10 (3)	5 (6)	3 (3)	6 (3)	9 (5)
Pneumonia	7 (2)	9 (2)	1 (1)	5 (5)	6 (3)	5 (3)
COVID-19[1]	3 (<1)	5 (1)	1 (1)	1 (1)	6 (3)	9 (5)
Pulmonary embolism	6 (2)	11 (3)	2 (2)	5 (5)	1 (<1)	3 (2)
Patients with adverse events of special interest, n (%)						
Serious infections	50 (13)	58 (15)	12 (13)	17 (19)	37 (21)	29 (17)
Cytokine release syndrome	0	2 (<1)	0	1 (1)	3 (2)	1 (<1)
Serious hypersensitivity reactions	1 (<1)	1 (<1)	1 (1)	0	0	0
Infusion site reactions	1 (<1)	1 (<1)	1 (1)	0	0	0
Neutropaenia	1 (<1)	0	0	0	0	0

[1]COVID-19, as per protocol, was only to be reported as an adverse event if the signs and symptoms of COVID-19 were more severe than expected.

MODS, multiple organ dysfunction syndrome.

References

1. Rochwerg B, Agarwal A, Siemieniuk RA*, et al.* A living WHO guideline on drugs for covid-19. BMJ 2020; 370: m3379.
2. Schulte-Schrepping J, Reusch N, Paclik D*, et al.* Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment. Cell 2020; 182: 1419-1440.e1423.
3. Liao M, Liu Y, Yuan J*, et al.* Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nature Medicine 2020; 26: 842-844.
4. Schurink B, Roos E, Radonic T*, et al.* Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe 2020; 1: e290-e299.
5. Hazeldine J, Lord JM. Immunesenescence: A Predisposing Risk Factor for the Development of COVID-19? Front Immunol 2020; 11: 573662.
6. Pietrobon AJ, Teixeira FME, Sato MN. Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Front Immunol 2020; 11: 579220.
7. Salje H, Tran Kiem C, Lefrancq N*, et al.* Estimating the burden of SARS-CoV-2 in France. Science 2020; 369: 208-211.
8. Bonanad C, García-Blas S, Tarazona-Santabalbina F*, et al.* The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects. J Am Med Dir Assoc 2020; 21: 915-918.
9. Centers for Disease Control and Prevention. Risk for COVID-19 Infection, Hospitalization, and Death By Age Group. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Date last accessed: 26 November 2021.
10. Lang FM, Lee KMC, Teijaro JR*, et al.* GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. Nat Rev Immunol 2020; 20: 507-514.
11. 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: 822-830.
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. Sci Immunol 2021; 6: eabg9873.
13. Zhou Y, Fu B, Zheng X*, et al.* Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Nat Sci Rev 2020: nwaa041.

14. 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.
15. Hue S, Beldi-Ferchiou A, Bendib I*, et al.* Uncontrolled Innate and Impaired Adaptive Immune Responses in Patients with COVID-19 Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2020; 202: 1509-1519.
16. Buckley CD, Simón-Campos JA, Zhdan V*, et al.* Efficacy, patient-reported outcomes, and safety of the anti-granulocyte macrophage colony-stimulating factor antibody otilimab (GSK3196165) in patients with rheumatoid arthritis: a randomised, phase 2b, dose-ranging study. Lancet Rheumatology 2020; 2: e677-e688.
17. World Health Organization. R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf. Date last accessed: 9 August 2022.
18. Vincent JL, Moreno R, Takala J*, et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22: 707-710.
19. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J Pharmacokinet Pharmacodyn 2001; 28: 507-532.
20. Asch DA, Sheils NE, Islam MN*, et al.* Variation in US Hospital Mortality Rates for Patients Admitted With COVID-19 During the First 6 Months of the Pandemic. JAMA Intern Med 2021; 181: 471-478.
21. Davies NG, Jarvis CI, van Zandvoort K*, et al.* Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature 2021; 593: 270-274.
22. Genovese MC, Berkowitz M, Conaghan PG*, et al.* MRI of the joint and evaluation of the granulocyte–macrophage colony-stimulating factor–CCL17 axis in patients with rheumatoid arthritis receiving otilimab: a phase 2a randomised mechanistic study. Lancet Rheumatol 2020; 2: e666-e676.
23. Williamson EJ, Walker AJ, Bhaskaran K*, et al.* Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020; 584: 430-436.

24. Recovery Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021; 397: 1637-1645.
25. Liu J, Liu Y, Xiang P*, et al.* Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of Translational Medicine 2020; 18: 206.
26. Hazeldine J, Lord JM. Neutrophils and COVID-19: Active Participants and Rational Therapeutic Targets. Frontiers in Immunology 2021; 12.
27. Wicks IP, Roberts AW. Targeting GM-CSF in inflammatory diseases. Nat Rev Rheumatol 2016; 12: 37-48.
28. Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell 2021; 184: 1671-1692.
29. Huang C, Huang L, Wang Y*, et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet 2021; 397: 220-232.
30. Temesgen Z, Burger CD, Baker J*, et al.* Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebo-controlled trial. Lancet Respir Med 2021.
31. Qiang X, Zhu S, Li J*, et al.* Monoclonal antibodies capable of binding SARS-CoV-2 spike protein receptor-binding motif specifically prevent GM-CSF induction. J Leukoc Biol 2022; 111: 261-267.
32. 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: 198.192-199.
33. Kiniksa Pharmaceuticals. Kiniksa Announces Results from Phase 3 Trial of Mavrilimumab in COVID-19-Related ARDS. 2021.
34. Fisher BA, Veenith T, Slade D*, et al.* Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial. Lancet Respir Med 2021.
35. Temesgen Z, Burger C, Baker J*, et al.* C-reactive protein as a biomarker for improved efficacy of lenzilumab in patients with COVID-19: Results from the LIVE-AIR trial. Chest 2021; 160: A2522-A2524.

36. Humanigen Inc. Humanigen Receives Preliminary Topline Data From NIH/NIAID Study of Lenzilumab in ACTIV-5/BET-B. 2022.
37. Clinicaltrials.gov. Efficacy and Safety of GSK3196165 (Otilimab) Versus Placebo and Sarilumab inParticipants With Moderately to Severely Active Rheumatoid Arthritis Who Havean Inadequate Response to Biological Disease-modifying Antirheumatic Drug(DMARDs) and/or Janus Kinase (JAK) Inhibitors (contRAst 3). https://clinicaltrials.gov/ct2/show/NCT04134728. Date last accessed: 16 February 2022.
38. Clinicaltrials.gov. Efficacy and Safety of GSK3196165 Versus Placebo and Tofacitinib in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate (contRAst 1) (NCT03980483). https://www.clinicaltrials.gov/ct2/show/NCT03980483. Date last accessed: 16 February 2022.
39. Clinicaltrials.gov. Efficacy and Safety of GSK3196165 Versus Placebo and Tofacitinib in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Conventional Synthetic (cs)/Biologic (b) Disease Modifying Anti-rheumatic Drugs (DMARDs) (contRAst 2) (NCT03970837). https://clinicaltrials.gov/ct2/show/NCT03970837. Date last accessed: 16 February 2022.

Figure 1. CONSORT flow diagram in OSCAR study Part 1 (A) and Part 2 (B). *Patients may have more than one reason for failure. AE, adverse event; ITT, intent-to-treat.

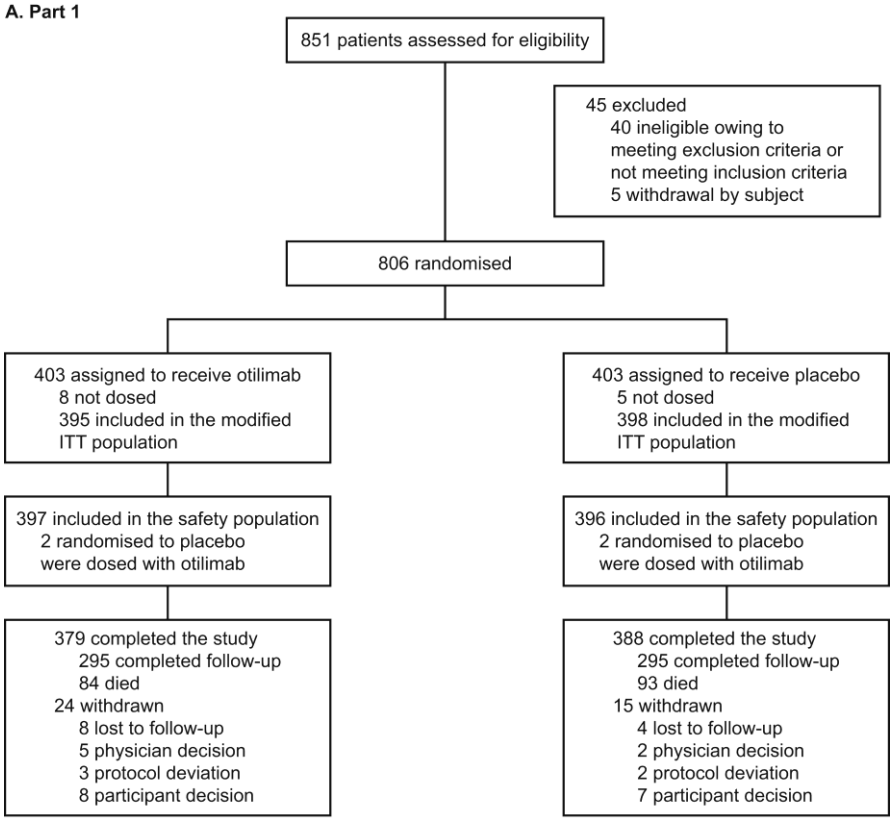
Figure 2. Proportion of patients alivFigure 5. Kaplan–Meier time to all-cause mortality up to Day 60 in the mITT population (A) and post hoc 70–
79 year age group (B) of Part 1, and in the mITT population of Part 2 (C) (secondary endpoint). mITT, modified intent-to-treat.e and free of respiratory failure at Day 28 in Part 1 (A) and Part 2* (B) (primary endpoint). *Analysis of the primary endpoint in patients by clinical status at baseline stratified by age group was not conducted in Part 2 due to the low number of patients aged ≥80 years. CI, confidence interval.

Figure 3. All-cause mortality in Part 1 (A) at Day 28 (post hoc*) and Day 60 (prespecified), and in Part 2 at Day 28 and Day 60 (B, prespecified). *Day 28 analysis in Part 1 was conducted post hoc, thus data are not available by clinical status at baseline. CI, confidence interval.

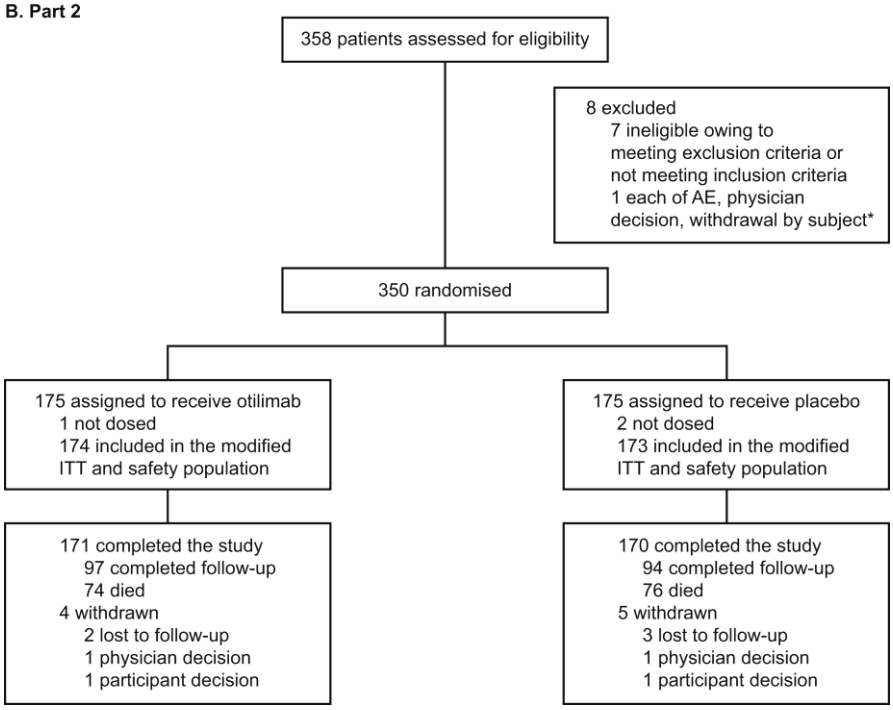
Figure 4. Kaplan–Meier time to recovery from respiratory failure up to Day 28 in the mITT population (A) and post hoc 70–79 year age group (B) of Part 1, and in the mITT population of Part 2 (C) (secondary endpoint). mITT, modified intent-to-treat.

Figure 5. Kaplan–Meier time to all-cause mortality up to Day 60 in the mITT population (A) and post hoc 70–79 year age group (B) of Part 1, and in the mITT population of Part 2 (C) (secondary endpoint). mITT, modified intent-to-treat.

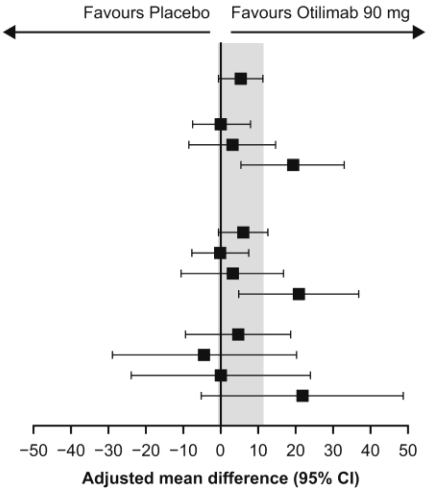
A. Part 1



B. Part 2

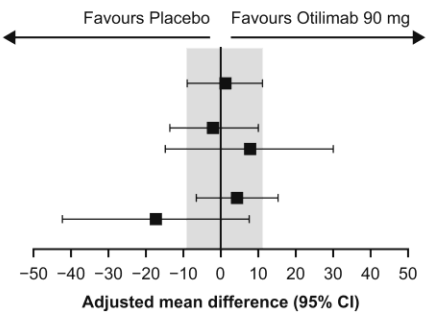


A. Part 1



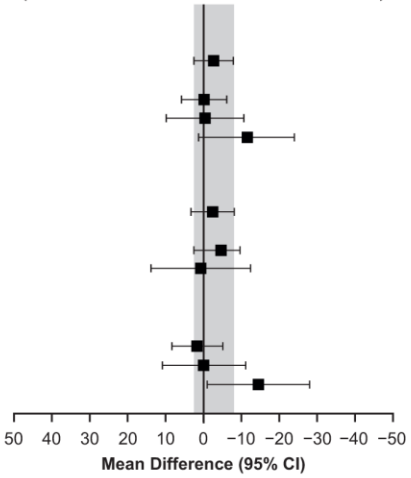
	Otilimab (N=395) n1/n2 (%)	Placebo (N=398) n1/n2 (%)	Adjusted Mean Difference (95% CI)
Primary Endpoint			
Overall	**277/389 (71)**	**262/393 (67)**	**5.3 (−0.8, 11.4)**
Age Group			
<60 years	141/171 (82)	148/179 (83)	0.2 (−7.7, 8.1)
60–<70 years	79/131 (60)	72/123 (59)	3.0 (−8.7, 14.8)
70–79 years	57/87 (66)	42/91 (46)	19.1 (5.2, 33.1)
Clinical Status at Baseline			
Category 5			
Overall	**233/302 (77)**	**218/303 (72)**	**5.9 (−0.8, 12.7)**
<60 years	125/144 (87)	127/146 (87)	−0.2 (−7.9, 7.6)
60–<70 years	62/95 (65)	56/90 (62)	3.0 (−10.8, 16.9)
70–79 years	46/63 (73)	35/67 (52)	20.8 (4.6, 37.0)
Category 6			
Overall	**44/84 (52)**	**43/88 (49)**	**4.6 (−9.6, 18.8)**
<60 years	16/27 (59)	21/33 (64)	−4.4 (−29.1, 20.4)
60–<70 years	17/34 (50)	16/32 (50)	0.0 (−24.1, 24.1)
70–79 years	11/23 (48)	6/23 (26)	21.7 (−5.4, 48.9)

B. Part 2*



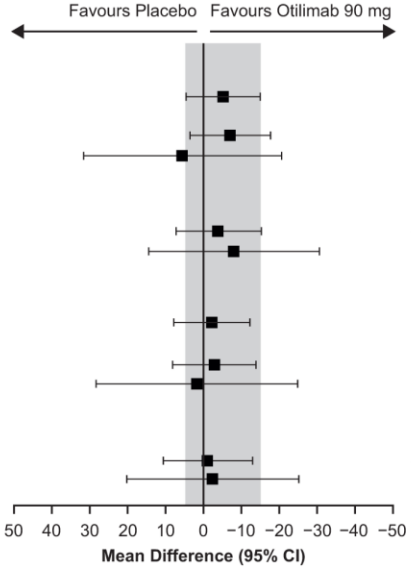
	Otilimab (N=174) n1/n2 (%)	Placebo (N=173) n1/n2 (%)	Adjusted Mean Difference (95% CI)
Primary Endpoint			
Overall	**89/172 (52)**	**87/170 (51)**	**0.9 (−9.3, 11.2)**
Age Group			
70–<80 years	65/124 (52)	72/133 (54)	−2.1 (−14.0, 9.8)
≥80 years	18/40 (45)	12/32 (38)	7.7 (−14.7, 30.2)
Clinical Status at Baseline			
Category 5	82/147 (56)	75/143 (52)	4.2 (−6.9, 15.4)
Category 6	7/25 (28)	12/27 (44)	−17.5 (−42.7, 7.6)

A.

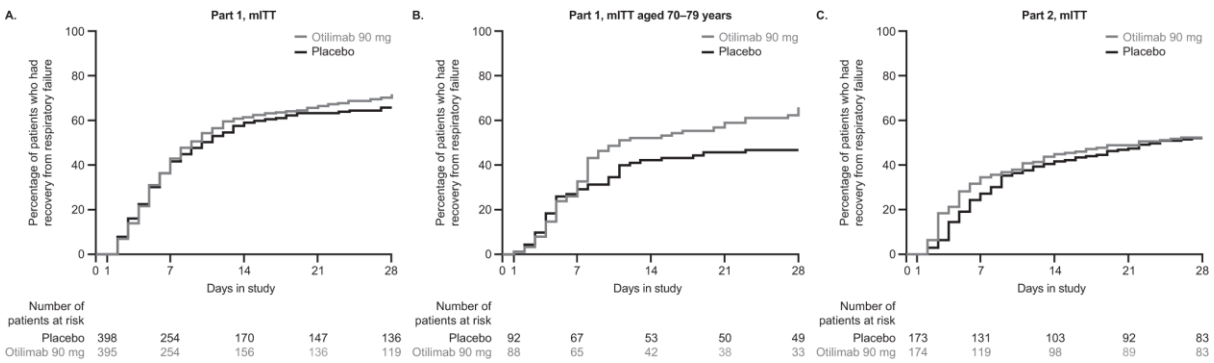


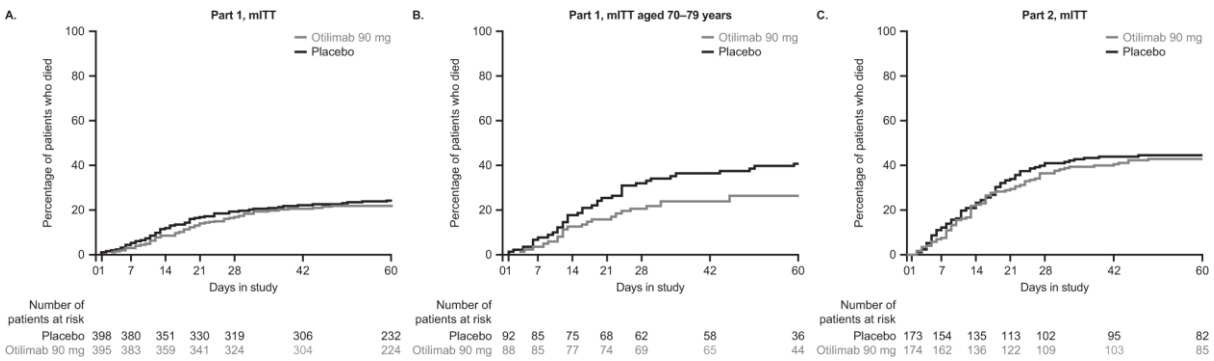
	Otilimab (N=395) n1/n2 (%)	Placebo (N=398) n1/n2 (%)	Adjusted Mean Difference (95% CI)
All-Cause Mortality			
Day 28			
Overall	**64/386 (17)**	**74/393 (19)**	**−2.6 (−7.8, 2.6)**
Age Group			
<60 years	15/168 (9)	16/179 (9)	−0.1 (−6.0, 5.8)
60–<70 years	31/131 (24)	29/123 (24)	−0.3 (−10.5, 10.0)
70–79 years	18/87 (21)	29/91 (32)	−11.3 (−24.0, 1.4)
Day 60			
Overall	**84/373 (23)**	**93/386 (24)**	**−2.4 (−8.0, 3.3)**
Clinical Status at Baseline			
Category 5	55/291 (19)	66/299 (22)	−3.5 (−9.6, 2.7)
Category 6	27/79 (34)	26/85 (31)	0.8 (−12.4, 14.0)
Age Group			
<60 years	22/162 (14)	20/176 (11)	1.8 (−5.0, 8.5)
60–<70 years	39/127 (31)	36/120 (30)	0.0 (−11.0, 11.0)
70–79 years	23/84 (27)	37/90 (41)	−14.4 (−27.9,−0.9)

B.



	Otilimab (N=174) n1/n2 (%)	Placebo (N=173) n1/n2 (%)	Mean Difference (95% CI)
All-Cause Mortality			
Day 28			
Overall	**63/172 (37)**	**70/170 (41)**	**−5.2 (−15.1, 4.7)**
Clinical Status at Baseline			
Category 5	51/147 (35)	58/143 (41)	−7.1 (−17.7, 3.6)
Category 6	12/25 (48)	12/27 (44)	5.6 (−20.6, 31.8)
Age Group			
70–<80 years	40/124 (32)	49/133 (37)	−3.9 (−15.3, 7.4)
≥80 years	21/40 (53)	19/32 (59)	−8.0 (−30.7, 14.6)
Day 60			
Overall	**74/171 (43)**	**76/170 (45)**	**−2.2 (−12.4, 7.9)**
Clinical Status at Baseline			
Category 5	62/146 (42)	63/143 (44)	−2.9 (−14.0, 8.1)
Category 6	12/25 (48)	13/27 (48)	1.7 (−24.9, 28.2)
Age Group			
70–<80 years	49/124 (40)	55/133 (41)	−1.2 (−13.1, 10.6)
≥80 years	23/39 (59)	19/32 (59)	−2.6 (−25.4, 20.2)


A.
Part 1, mITT
Otilimab 90 mg
Placebo
Percentage of patients who had recovery from respiratory failure
100
80
60
40
20
0
0 1 7 14 21 28
Days in study
Number of patients at risk
Placebo 398 254 170 147 136
Otilimab 90 mg 395 254 156 136 119
B.
Part 1, mITT aged 70–79 years
Otilimab 90 mg
Placebo
Percentage of patients who had recovery from respiratory failure
100
80
60
40
20
0
0 1 7 14 21 28
Days in study
Number of patients at risk
Placebo 92 67 53 50 49
Otilimab 90 mg 88 65 42 38 33
C.
Part 2, mITT
Otilimab 90 mg
Placebo
Percentage of patients who had recovery from respiratory failure
100
80
60
40
20
0
0 1 7 14 21 28
Days in study
Number of patients at risk
Placebo 173 131 103 92 83
Otilimab 90 mg 174 119 98 89 83


A.
Part 1, mITT
Otilimab 90 mg
Placebo
Percentage of patients who died
100
80
60
40
20
0
01
7
14
21
28
42
60
Days in study
Number of patients at risk
Placebo 398 380 351 330 319 306 232
Otilimab 90 mg 395 383 359 341 324 304 224
B.
Part 1, mITT aged 70–79 years
Otilimab 90 mg
Placebo
Percentage of patients who died
Days in study
Number of patients at risk
Placebo 92 85 75 68 62 58 36
Otilimab 90 mg 88 85 77 74 69 65 44
C.
Part 2, mITT
Otilimab 90 mg
Placebo
Percentage of patients who died
Days in study
Number of patients at risk
Placebo 173 154 135 113 102 95 82
Otilimab 90 mg 174 162 136 122 109 103 85

Supplemental Materials

List of investigators and hospitals

Argentina

Sanatorio de La Trinidad Mitre, Buenos Aires, Argentina. Javier Altclas, MD, Mariana Patricia Berte, Adriana Victoria Diaz Balocchi, Maria Verónica Latini, Daniela Malano Barletta, Claudia Cristina Salgueira, MD, Analia Rosana Santa Maria.

Sanatorio Mayo Privado Sanatoria Allende S.A, Cordoba, Argentina. German Ambasch, MD, Jorge Luis Tambini Diaz.

Clinica Montegrande-Clinica Privada Monte Grande, Buenos Aires, Argentina. Pedro Xavier Bocca Ruiz, MD, Xavier Antonio Bocca Pereira, Sebastian Caravaggio, Victor Hugo Pecci, Feliciano Petro Moreno.

Clinca Privada Colombo, Cordoba, Argentina. Hugo Raul Colombo, MD, PhD, Marianela Colombo.

Clínica Privada Independencia de Munro, Buenos Aires, Argentina. Pablo Alexis Christian Doreski, MD, MBA, Jorge Oscar Fandi, Celia Sara Giler, Fernando Ricardo Racca Velasquez, Damian Gonzalo Rutolo, Oscar Alberto Salva.

Instituto de Cardiologia Juana F. Cabral, Corrientes, Argentina. Angel Esteban Piacenza, M.D, Leonardo Mariano Braccini, Jorge Matias Ochoa.

Sanatorio Allende S.A., Córdoba, Argentina. Fernando Oscar Riera, MD, Aldana Mano, Gabriela Virginia Peukert, Carlos Federico Romero.

Belgium

CHU Dinant Godinne, Cliniques Universitaires Catholic University of Louvain Namur, Yvoir, Belgium. Nathalie Ausselet, MD, Pierre Bulpa, MD, Benedicte MJB, Delaere, MD, Alain M. Dive, MD, Patrick Evrard, MD, Geoffrey Horlait, MD, Isabelle Michaux, MD, Pascal Reper, MD.

UZ Brussel, Brussels, Belgium. Elisabeth De Waele, MD, PhD, Marc W. Diltoer, MD, PhD, Steven Hendrickx, Joop Jonckheer, MD, Michael Mekeirele, MD, Duc Nam Nguyen, MD, PhD, Matthias Raes, MD, Simon de Ridder, MD, Alex R. Van Hoorn, Ruth Van Lacker, Wout Van Oosterwyck, Domien Vanhonacker, MD.

Brazil

Hospital São Paulo – UNIFESP, São Paulo, Brazil. Jaquelina Sonoe Ota Arakaki, MD, PhD, Oliver Augusto Nascimento, Daniella Silva de Almeida.

Santa Casa de Misericordia de Belo Horizonte, Belo Horizonte, Brazil. Antonio Tarcisio Freire, MD, Thayse Kayser, Claudia Oliveira.

Instituto de Infectologia Emilio Ribas, São Paulo, Brazil. Luiz Carlos Pereira Junior, MD, Amanda Bittencourt, Gustavo Dittmar, Bernardo Porto Maia, Denise Pacola, Vistor Passarelli, Maria Silvia Biagioni Santos, Tamara Newman Lobato Azevedo Souza, Ana Luiza de Castro Conde Toscano.

Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. Esper Georges Kallas, MD, PhD, Angela Carvalho Freitas, Gabriel Fialkovitz da Costa Leite, Lucas Chaves Netto.

Universidade Federal de Minas Gerais, Minas Gerais, Brazil. Jorge Andrade Pinto, MD, Thiago Bragança Lana Silveira Ataide, Renan Detoffol Bragança, Helena Duani, Flavia Gomes Faleiro Ferreira.

Rua Oswaldo Oscar Barthelson, Campinas, Brazil. José Francisco Saraiva, MD, Matheus Nascimento, Hugo Bertipaglia.

Hospital Alemão Oswaldo Cruz, Hospital Sirio Libanes Instituto de Ciências, São Paulo, Brazil. Victor Augusto Hamamoto Sato, MD, Daniela Ghidetti Mangas Catarino, Jose Victor Gomes Costa, Erico Souza De Oliveira, MD, Bernadete Ferreira, Sara Mohrbacher, MD, Leonardo Victor Barbosa Pereira, MD, PhD.

Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Eduardo Sprinz, MD, PhD, MSc, Gustavo Leal Agune, Beatriz Arns, Giulia Baldissera, Ana Elize Barin, Murillo Machado Cipolat, Julio Cezar Gonçalves Cordeiro dos Santos, Mariana Falcetta, Leonardo Martins Pires, Guilherme Geraldo Lovato Sorio, Tarsila Vieceli.

Canada

Hôpital du Sacré Cœur de Montréal, Montréal, Québec, Canada. Martin Albert, MD, Francis Bernard, Yiorgos Alexandros Cavayas, MD, Karim Serri, David Williamson.

UBC James Hogg Research Centre Saint Paul's Hospital, Vancouver, British Columbia, Canada. John Boyd, MD, Adam Peets, Demetrios Sirounis.

The Ottawa Hospital, Ottawa, Ontario, Canada. Shane W. English BSc, MD, FRCPC, MSc, Scott J Millington, MD, FRCPC.

CISSS de la Montérégie-Centre/Hôpital Charles Le Moyne, Taschereau, Québec, Canada. Germain Poirier, MD, CM, FRCPC, Antoine Delage, Louise Passerini.

Unite de recherche Clinique du CISSS des Laurentides, Saint-Jerome, Québec, Canada. Sebastien Poulin, MD, Louay Mardini, MD, Yves Pesant, MD.

Chile

Hospital Barros Luco, Santiago, Chile. Luis Benito Fuenzalida Castillo, Ronald Edgar Pairumani Medrano, MD.

Clinica Las Condes, Las Condes, Santiago, Chile. Tomas Regueira Heskia, MD, PhD, Andrés Alberto Ferre Contreras, MD.

Centro Respiratorio Integral Ltda, Region de Valparaiso, Chile. Juana Rosa Pavie Gallegos, MD, Patricia Alexandra Intriago Alcivar, Baird Ibn Zegpi Keller, MD.

Hospital Regional de Talca, Región Del Maule, Chile. Absalón Rafael Sergio Silva Orellana, MD, Carolina Paz González Navarro, MD.

Columbia

Hospital Universitario San Ignacio, Bogotá, Colombia. Luis Carlos Triana Moreno, Stela del Pilar Baracaldo Gomez, MD, Maria Alejandra Betancur Diaz, MD, Angel Alberto Garcia, MD.

France

HCL – Centre Hospitalier Lyon Sud, Pierre-Bénite, France. Bernard Allaouchiche, MD, PhD, Marie Darien, MD, Donatien De Seissan De Marignan, MD, Marion Didier, MD, Lucille Jay,

MD, Emilie Joffredo, MD, Maxime Lecocq, MD, Alain Lepape, MD, Mélanie Levrard, MD, Fabrice Thiolliera, MD, Florent Wallet, MD.

CHU d'Angers, Angers, France. Pierre Asfar, MD, PhD, François Beloncle, MD, Julien Demiselle, MD, Hélène Julien, MD, Achille Kouatchet, MD, Satar Mortaza, MD, Pierre-Yves Olivier, MD, Marc Pierrot, MD, Vincent Souday, MD.

CH Valenciennes - Hôpital Jean Bernard, Valenciennes, France. Hatem Boughanmi, MD, Fabien Lambiotte, MD, Piehr Saint Leger, MD.

GH Pitié-Salpêtrière, Paris, France. Jean-Michel Constantin, MD, PhD, Mona Assefi, MD, Marine Le Corre, MD, Bao-Long Nguyen, MD, Cyril Quemeneur, MD, Guillaume Savary, MD, Agathe Selves, MD.

Centre Hospitalier Universitaire de Limoges, Limoges, France. Bruno François, MD, Thomas Daix, MD, Arnaud Desachy, MD, Bruno Evrard, MD, Anne-Laure Fedou, MD, Guillaume Gilbert, MD, Marine Goudelin, MD, Amandine Sanson, MD, Julien Vaidie, MD, Philippe Vignon, MD, PhD.

CHR de Metz-Thionville – Hôpital Mercy, Service de Réanimation Polyvalente, Ars-Laquenexy, France. Rostane Gaci, MD, Cyril Cadoz, MD, Serge Le Tacon, MD, Guillame Louis, MD, Adeline Perrein, MDCHD Vendée – Site De La Roche-sur-Yon, La Roche-Sur-Yon, France. Jean-Claude Lacherade, MD, Marie-Ange Azais, MD, Konstantinos Bachoumas, MD, Rémi Bernardon, MD, Gauthier Blonz, MD, Gwenhaël Colin, MD, Luc Desmedt, MD, Maud Fiancette, MD, Matthieu Henry-Lagarrigue, MD, Hugo Hille, MD, Christine Lebert, MD, Laurent Martin-Lefevre, MD, Caroline Pouplet, MD, Aurélia Toussaint, MD, Isabelle Vinatier, MD, Aihem Yehia, MD.

CHU Amiens-Picardie - Site Sud, Amiens, France. Julien Maizel, MD, PhD, Abdallah Al Salameh, MD, Damien Basille, MD, Mélanie Drucbert, MD, Mathieu Guilbart, MD, Jean-Philippe Lanoix, MD, Michel Slama, MD, Sandrine Soriot-Thomas, MD, Yoann Zerbib, MD.

Hôpitaux Universitaires de Strasbourg - Nouvel Hôpital Civil, Strasbourg, France. Ferhat Meziani, MD, PhD, Jessy Cattelan, M.D., Raphaël Clere-Jehl, MD, Julien Demiselle, MD, Julie Helms, MD, Louise-Marie Jandeaux, MD, Christine Kummerlen, MD, Hamid Merdji, MD, Alexandra Monnier, MD, Hassene Rahmani, MD, Antoine Studer, MD.

Groupe Hospitalier Sud Ile de France, Melun, France. Mehran Monchi, MD, Esther Mbakulu Muanda, MD, Franck Pourcine, MD.

Centre Hospitalier Victor Dupouy, Argenteuil, France. Gaëtan Plantefeve, MD, Damien Contou, MD, Megan Fraisse, MD, Paul Desaint, MD, Elsa Logre, MD, Olivia Picq, MD, Florence Sarfati, MD, Joanna Tirolien, MD.

Hôpitaux Universitaires de Strasbourg - Hôpital de Hautepierre, Service de Médecine Intensive et Réanimation, Strasbourg, France. Francis Schneider, MD, PhD, Mathieu Baldacini, MD, Thien Nga Chamaraux, MD, Pierre Diemunsch, MD, Sophie Diemunsch, MD, Max Guillot, MD, Jean-Etienne Herbrecht, MD, Pierre-Olivier Ludes, MD, Guillaume Morel, MD, Eric Noll, MD, Julien Pottecher, MD.

CHU Grenoble Alpes – Site Nord La Tronche - Hôpital Michallon, La Tronche, France. Nicolas Terzi, MD, Joanna Bougnaud, MD, Anaïs Dartevel, MD, Louis-Marie Galerneau, MD, Côme Gerard, MD, Guillaume Rigault, MD, Carole Schwebel, MD, Florian Sigaud, MD.

Germany

University Hospital Aachen, Department of Pneumology and Critical Care, Nordrhein-Westfalen, Germany. Michael Dreher, MD, Maria Aetou MD, Christian Cornelissen, MD, Ayham Daher, MD, Alexander Kersten, MD, Tobias Mueller, MD, Annegret Mueller, MD, Judith Smith, MD, Robert Stoehr, MD.

Universitaetsmedizin Goettingen, Goettingen, Germany. Onnen Moerer, MD, Martin Winkler, MD.

Medizinische Hochschule Hannover, Hospital of Pneumology, Hannover, Niedersachsen, Germany. Tobias Welte, MD, Torben Brod, MD, Nora Drick, MD.

Krankenhaus Merheim, Koeln, Nordrhein-Westfalen, Germany. Wolfram Windisch, MD, Laura Emrich, MD, Danial Majorski, MD, Sarah Schwarz, MD, Maximillian Wollsching-Strobel, MD.

Charité - Universitätsmedizin Berlin, Berlin, Germany. Martin Witzenrath, MD, Phillipp Enghard, MD, Moritz Mueller-Plathe, MD.

India

Max Smart Super Speciality Hospital (A Unit of Gujarmal Modi Hospital and Research Centre for Medical Sciences), New Delhi, India. Ritesh Aggarwal, MBBS, DNB, Arun Dewan.

Medica Superspecialty Hospital, Kolkata, India. Tanmay Banerjee, MD, MBBS, Anirban Bose, MD, Amitabha Saha, MD.

Government Medical College, Aurangabad, India. Meenakshi Bhattacharya, MD, MBBS, Aditya Gudhate, Avinash Humbe.

Saint Theresas Hospital, Hyderabad, India. Nagaraju Boyilla, MD, MBBS, Akula Venkateshwar Rao.

Government Medical College and Hospital Nagpur, Nagpur, India. Dipti Chand, MD, MBBS, Nikhil Agarwal, Chandrashekhar Atkar, Sagar Khandare.

Metas Adventis Hospital, Surat, India. Chirag Chhatwani, MD, MBBS, Amit Shah, Ramesh Surati.

Peerless Hospitex Hospital and research center limited, Kolkata, India. Rimita Dey, MD, MBBS, Subhrojyoti Bhowmik, MD.

Kasturba Hospital for Infectious Disease, Mumbai, India. Ajay Jhaveri, MBBS, DNB, Chandrakant Pandurang Pawar, MD.

Noble Hospital Private Limited, Pune, India. Reema Kashiva, MD, MBBS, Prashant Raghunath Potdar.

SMS Medical College and Attached Hospitals Jaipur, Jaipur, India. Chhuttan Lal Nawal, MD, MBBS, Radhey Shyam Chejara, MD, Vinaykumar Meena, MD, Hazari Lal Saini, MD.

MGM Medical College and Hospital, Aurangabad, India. Umar Quadri Syed, MD, MBBS, Rohit Jacob, Nilofer Bano Patel.

Ruby Hall Clinic, Cancer Centre, Pune, India. Kapil Zirpe, MD, Abhijit Deshmukh.

Italy

Istituto Nazionale Malattie Infettive – INMI L. Spallanzani IRCCS, U.O.C. Immunodeficienze Virali, Roma, Italy. Andrea Antinori MD, Marta Camici, Ilaria Mastrorosa, Valentina Mazzotta, Carmela Pinnetti, Alessandra Vergori.

Fondazione S. Raffaele del Monte Tabor, Unita' di Reumatologia e Immunologia Clinica, Divisione di Medicina, Milano, Italy. Lorenzo Dagna, MD, Alessandro Tomelleri.

AO Ospedali dei Colli, 1 UTSIR COVID, Napoli, Italy. Guiseppe Fiorentino, MD, Anna Annuzianta, Novella Carannante, Valentina Si Spirito, Pasquale Imitazione, Maurizia Lanza, Antonelle Marotta, Giorgio Emanuele Polistina.

Azienda Ospedaliero-Universitaria "Policlinico Riuniti" di Foggia, Dipartimento di Medicina Specialistica, Foggia, Italy. Maria Pia Foschino Barbaro, MD, Donato Lacedonia, Giorgia Lepore, Carla Maria Irene Quarato, Pasquale Tondo.

Ospedale Luigi Sacco – Azienda Ospedaliera e Polo Universitario, Dipartimento Malattie Infettive 1° Divisione Malattie Infettive ed Allergologia, Milan, Italy. Giuliano Rizzardini, MD, Amedeo F. Capetti, MD, Massimo Coen, Maria V Cossu, MD, Ivano Faggion, Guido Gubertini, Matteo Passerini, Monica Schiavini.

Japan

Shonan Fujisawa Tokushukai Hospital, Kanagawa, Japan. Makoto Hibino, MD, Shigeto Horiuchi, Tetsuri Kondo, Kazunari Maeda, Shunichi Tobe.

Tokyo Nishi Tokushukai Hospital, Tokyo, Japan. Hirokazu Iijima, MD, Ryo Ga, Mutsuo Takaki.

Funabashi Central Hospital, Internal Medicine, Chiba, Japan. Satoru Ishikawa, MD, Akira Kojima.

National Center for Global Health and Medicine, Tokyo, Japan. Shinyu Izumi, MD, PhD, Kazuo Hakkaku, Masao Hashimoto, Masayuki Hojo, Motoyasu Iikura, Takashi Katsuno, Kazuki Kawajiri, Yusaku Kusaba, Ayako Mikami, Momoko Morishita, Chie Morita, Go Naka, Susumu Saito, Keita Sakamoto, Yuriko Sugiura, Manabu Suzuki, Jin Takasaki, Hiroshi Takumida, Yoshie Tsujimoto, Akinari Tsukada, Hiromu Watanabe, Yoh Yamaguchi.

Japanese Red Cross Medical Center, Tokyo, Japan. Takehiro Izumo, PhD, MD, Nobuyasu Awano, Kazushi Fujimoto, Munehiro Hayashi, Minoru Inomata, Yu Ito, Yuji Kondo, Kana Kono, Naoyuki Kuse, Kenro Maki, Haruko Mastsumoto, Yuta Moroe, Shun Muramatsu, Yutaka Muto, Akira Nomi, Shogo Sagisaka, Ayae Saiki, Keita Sakamoto, Kohei Takada, Mari Tone, Ryuta Yamashita, Tomoyuki Yamashita.

Yokohama City Minato Red Cross Hospital, Kanagawa, Japan. Isao Nagata, MD, Michiko Fujisawa, Shinsuke Karatsu, Eisaku Nashiki, Kei Sugiki, Taketo Suzuki, Tetsuhiro Takei, Hiroyuki Yamada, Naoki Yonezawa.

Nozaki Tokushukai Hospital, Neurosurgery, Osaka, Japan. Hidemitsu Nakagawa, MD, Shin Hirayama, Masakazu Tamura, Masanobu Yamada.

Tokyo Medical and Dental University, Tokyo, Japan. Yasuhiro Otomo, MD, Akira Endo, Kenichi Hondo, Takahiro Mitsumura, Yasunari Miyazaki, Koji Morishita, Kanae Ochiai, Keisuke Suzuki, Wataru Takayama.

Tokyo Shinjuku Medical Center, Tokyo, Japan. Hidefumi Shimizu, MD, Yoshimasa Horie, Hiroshi Kojima, Akira Mizoo.

Osaka City General Hospital, Osaka, Japan. Michinori Shirano, MD, PhD, Tomohiro Asaoka, Tetsushi Goto, Ko Iida, Keiji Konishi, Hidenori Nakagawa.

Saitama Medical University Hospital, Saitama, Japan. Norihito Tarumoto, MD, Kazuo Imai, Noriomi Ishibashi, Shigefumi Maesaki, Jun Sakai.

Fujita Health University Hospital, Aichi, Japan. Norimichi Uenishi, MD, Daichi Arakaki, Yohei Doi, Kenichiro Fujii, Masaya Hibino, Takao, Yuki Osuki, Hirotaka Otake.

Mexico

Fundacion Santos y de la Garza Evia I.B.P. Hospital San José TecSalud, Monterrey, Mexico. José-Fernando Castilleja-Leal, MD, Daniel Davila-Gonzalez, Alberto Garcia-Vega, Arturo Adrian Martinez-Ibarra, Juan Francisco Moreno-Hoyos Abril.

Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico. Pedro Martinez-Ayala, MD, Sara-Alejandra Aguirre-Diaz, Alfredo Gutierrez-Marin.

Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”, Mexico City, Mexico. Amy-Bethel Peralta-Prado, MD, Victor Hugo Ahumada-Topete, Maria Isabel Leon-Rodriguez.

Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico. Juan Gerardo Sierra-Madero, MD, Claudia Paola Alarcon-Murra, Jose Guillermo Dominguez-Cherit, Karen-Aranza Marañon-Solorio, Bernardo Alfonso Martínez-Guerra, Carlos Torruco-Sotelo.

Netherlands

Medisch Spectrum Twente, Enschede, Netherlands. Albertus (Bert) Beishuizen, MD, PhD, Alexander D. Cornet, MD, PhD, Bob Oude Velthuis, MD, Jan W. Vermeijden, MD, PhD.

Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands. Oscar Hoiting, MD, Marco A.A. Peters, MD, Els Rengers, MD.

Jeroen Bosch Ziekenhuis, Den Bosch, Netherlands. Frans W. (Wim) Rozendaal, MD, Cornelis P.C. de. Jager, MD, PhD, Miriam A.M. Moviat, MD, PhD, Anne J. Paling, MD, Florens N. Polderman, MD, G.A.M. (Astrid) Salet, MD, Koen S. Simons, MD, PhD.

Amphia Ziekenhuis, Breda, Netherlands. Simone van der Sar, MD, Remco S. Djamin, MD, PhD, Klaas M. (Merijn) Kant, MD, Kornelis H. van der Leest, MD, PhD, Sander Talman, MD.

Ikazia Ziekenhuis, Rotterdam, Netherlands. Fenna J. Schoonderbeek, MD, PhD, Maaike Muller-Ekas, MD, Ralph V. Pruijsten, MD, Anna F.C. Schut-Houtgraaf, MD, PhD, Susanne Stads, MD, Walter van den Tempel, MD, Henriette F.E.M. Willems, MD.

Peru

Clínica Internacional - Seda Lima, Lima, Peru. José Luis Cabrera Rivero, Alfredo Gilberto Guerreros Benavides, Edwin Hernando Herrera Flores, MD, Eneyda Giuvanela Llerena Zegarra, Lorena Mata Juarez, Teresa Jhovina Perez Rodriguez, Raúl Ruiz Castellanos, MD, Karla Ysabel Sánchez Vallejos, MD, Hernando Torres Zevallos, MD.

Centro de Investigación del Hospital Militar Central, Lima, Peru. Victoria Chavez Miñano, MD, Aida Miluska Delgado Flores, Raul Ernesto Porras Serna, Giovanna Rosa Trujillo Velita, MD.

Hospital Nacional Alberto Sabogal Sologuren, Lima, Peru. Luis Enrique Hercilla Vásquez, MD, Erika Cecilia Agurto Lescano, Ysabel Marlene Chavez Santillan, Ronald Nilton Guzman Ramos, Freddy Roberto Marchand Gago, Fernando Franz Namuche Ojeda, D'yanira Felieva Rojas Montaño, Miguel Angel Tapia Paredes, Carmen Sara Terrazas Obregon, MD, Nora Isabel Villoslada Contreras.

Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru. Fernando Cruz Mendo Urbina, MD, Oscar Melitón Reyna Vargas, Jose Carlos Ruelas Figueroa.

Poland

Wojewodzki Szpital Obserwacyjno-Zakazny, Bydgoszcz, Poland. Dorota Anna Dybowska, MD, PhD, Dorota Kozielewicz, Przemyslaw Slomkowski.

Centralny Szpital Kliniczny MSWiA w Warszawie, Warszawa, Poland. Andrzej M. Fal, MD, PhD, Kamil Adamczyk, Malgorzata Dorobek, Maciej Jankowski, Anna Jasinska, Antoni Okninski, Iwona Pikto-Pietkiewicz, Katarzyna Przybylowska, MD, Monika Maria Swiderska, Ewa Szczesniak, Konstanty Szuldrzynski, Rafal Wojtowicz, Justyna Zielinska-Turek.

Wielospecjalistyczny Szpital Miejski im. J. Strusia, City Hospital of Poznan, Poznan, Poland. Blazej Rozplochowski, MD, PhD, Teresa Ganowicz-Kaatz, Jakub Kopaczynski, Sylwia Michalik, Iwona Mozer-Lisewska, Maja Szczerbakowska.

Szpital Uniwersytecki w Krakowie, Oddzial Kliniczny Chorob Zakaznych, Krakow, Poland. Wojciech Serednicki, MD, PhD, Tomasz Gazda, Teresa Kowal, Anna Kwinta, Rafal Swistek, Wojciech Szpunar.

Wojewodzki Szpital Specjalistyczny im. J. Gromkowskiego, Oddzial Chorob Zakaznych ul, Wroclaw, Poland. Krzysztof Simon, MD, PhD, Justyna Janocha, Anna Szymanek-Pasternak, Aleksander Zinczuk.

Russian Federation

Clinic of Bashkir State Medical University, Ufa, Russian Federation. Bulat Bakirov, MD, PhD, Ruslan Maier, MD.

State Budget Healthcare Institution City Clinical Hospital #15 n.a. O.M.Filatov, Moscow, Russian Federation. Ivan G. Gordeev, MD, PhD, Vitaliy Firstov, Vartan Grigoryan, Ilia Kokorin, Ksenia Komissarova, Anna Kozlova, Nina Lapochkina, MD, Sevinch Mamedguseyinova, MD, Ksenia Polubatonova, MD, Natalia Alexandrovna Suvorova, MD.

Regional Clinical Hospital #4, Chelyabinsk, Russian Federation. Galina L Ignatova, MD, Vladimir Antonov MD, Olga V. Rodionova, MD.

Budgetary Healthcare Institution of the Voronezh region 'Voronezh Regional Clinical Hospital #1,' Voronezh, Russian Federation. Natalia E. Kostina, MD, PhD, Svetlana Chuprina, MD, Olga M. Korolkova, MD, PhD, Andrey Vorobyev, MD.

BUZ of Omsk Region, Regional Clinical Hospital, Omsk, Russian Federation. Tatiana Kropotina, MD, Julia Arbuzova, MD, Evgeniya Baygozina, MD, Elena Elokhina, MD, Irina Menschikova, MD, Ekaterina Shelyagina, MD, Boris Statsenko, MD, Yuliya Zakharevich, MD.

Nizhniy Novgorod City Clinical Hospital #10, Nizhniy Novgorod, Russian Federation. Ekaterina V. Makarova, MD, PhD, Ludmila Alexandrovna Lomakina, MD, Natalya Lyubavina, Vladimir Vakhlamov.

Saint Petersburg State Healthcare Institution City Mariinsky Hospital, Saint Petersburg, Russian Federation. Aleksey G. Mamonov, MD, Vladimir Okhritckii.

State Budget Institution of Health, City Hospital #5, Barnaul, Russian Federation. Tatiana Martynenko, MD, PhD, DNSc, Konstantin Gatalskiy, MD, Ilya Lazarenko, MD, Olga Paraeva, MD, Anastasiya Shek, Elena A Vasilkova, Olga Ganova, MD.

Perm Regional Clinical Hospital #1, Perm, Russian Federation. Yuliya Trefilova, MD, PhD, Galina Bykova, MD, Anna Ershova, MD, Natalia Grigoriadi, MD, Natalia Komarovskaya, MD, Kseniya Trenogina, MD, Vera Vustina, MD, Tatiana Yakovleva, MD, Yulia Zhelnina, MD.

City Clinical Hospital #14, Ekaterinburg, Russian Federation. Elena Mikhailovna Vishneva, MD, PhD, Ekaterina A. Egorova, MD, Anna Pavlovna Isakova.

South Africa

Jakaranda Hospital, Pretoria, South Africa. Johannes Breedt, MBChB, DOH.

MERC SiReN, Metcare Milpark Hospital, Johannesburg, South Africa. Natasha Joseph. MB ChB, Safiyya Chohan MB ChB, Shiraaz Bhamjee, MB ChB.

University of Stellenbosch, Cape Town, South Africa. Coenraad F.N. Koegelenberg, PhD, MB ChB, MMed, Brian William Allwood, MB ChB, PhD, Usha Lalla, MB ChB.

Durban International Clinical research site, Enhancing Care Foundation, Durban, South Africa. Rosie Mngqibisa, MB ChB, Umesh Gangharam Lalloo, MB ChB, Sajeeda Mawlana, MB ChB, Sundrapragasen Pillay, MB ChB, Natasha Lalloo, MB ChB.

Mzansi Ethical Research Centre – Middleburg, Middleburg, South Africa. Friedrich Georg Petrick. MB ChB, Augustine Chaumba, MB ChB, Gertruida Magdalena, MB ChB, Maxine Stephany Sampson, MB ChB, Mohammed Siddique Tayob, MB ChB.

Panorama Research, Cape Town, South Africa. Johan Theron, MB ChB, Daphne Charlotte Richter, MB ChB, Morne Johan Vorster, MB ChB.

Clinical Projects Research SA pty Ltd, Worcester, South Africa. Louis J. van Zyl, MB ChB, MMed, Marina Naude, MB ChB, Christo van Dyk, MB ChB, MMed, Francois H. van Zyl, MB ChB.

Life The Glynnwood Hospital, Eastrand Physicians, Benoni, South Africa. Agatha C. Wilhase, MB ChB, MCFP, MFamMed, Reece Boosi, MB ChB, Nabeela Kajee, MB ChB, MMed, Jayseelan Naidu, MB ChB, MMed, Kuven Naidu, MB ChB, Mirriam Patel, Bilaal Wadee, MB ChB

Spain

Hospital Universitario La Princesa, Madrid, Spain. Tamara Alonso Pérez, MD, María de Churruca Arróspide.

Hospital Universitario Gregorio Marañón, Madrid, Spain. Javier de Miguel Díez, MD, PhD, Walther Iván Girón Matute, Zichen Ji, Luis Puente Maestu, José Rafael Terán Tinedo.

H.E. Enferma Isabel Zendal, Madrid, Spain. Pedro Landete Rodríguez, MD, Clotilde Funes Moreno, Daniel Laorden Escudero, Eva Prats Gracia, José Rafael Terán Tinedo.

Hospital del Mar-IMIM, Barcelona, Spain. Rosana Muñoz Bermúdez, MD, PhD, Judith Marín Corral, MD, PhD, Francisco José Parrilla Gómez, MD, Clara Vilà Vilardell, MD.

Fundación Jiménez Díaz, Madrid, Spain. Germán Peces-Barba Romero, MD, PhD, Laura Álvarez Suárez, Elena Cabezas Pastor, Itziar Fernández Ormaechea, Andrés Giménez Velando, Carolina María Gotera Rivera, Pablo López Yeste, Marcel José Rodríguez Guzmán, Arnoldo de Jesús Santos Oviedo.

Hospital de San Pedro, Logroño, Spain. Carlos Ruíz Martínez, MD, PhD, Jorge Alba Fernández, Adolfo Calvo Martínez, Dolores del Puerto García, José Andrés Molina Espejo, Alejandra Roncero Lázaro, Esther Saiz Rodrigo, Javier Ugedo Urruela.

Hospital Universitario de Bellvitge, Barcelona, Spain. Salud Santos Pérez, MD, PhD, Ester Cuevas Sales, Mercè Gasa Galmes, Yolanda Ruiz Albert, Mikel Sarasate Azkona, Guillermo Rafael Suárez Cuartín, Pere Trias Sabrià.

Hospital Universitario Infanta Sofia, Madrid, Spain. Llanos Soler Rangel, MD, PhD, Miguel Ángel González Gallego, María Teresa Ramírez Prieto, Pilar Ruiz Seco, Inés María Suárez García, Miguel Ángel Vázquez Ronda.

United Kingdom

The James Cook University Hospital, Middlesbrough, United Kingdom. Stephen Bonner. MBBS, David Robert Chadwick, Nicola Cree, Uwe Franke, Isabel Gonzalez, Jeremy Henning, Alexander Scott, Michelle Shaw, Judith Wright.

Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom. John Isaacs, PhD, FRCP, BSc(Hon.), MBBS, Andrew Barr, Ian Clement, Iain McCullagh, David Ashley Price, Amada Sanchez Gonzalez.

Bradford Teaching Hospitals, Bradford Royal Infirmary, Bradford, United Kingdom. Tom Lawton, BM, BCh, MA, MSc, MRCP, FRCA, FFICM, James Morgan, Dinesh Saralaya, Paul Whitaker.

Wythenshawe Hospital, Manchester, United Kingdom. Andrew David Martin, MB ChB, MRCP, FRCA, FFICM, CCT, Peter David Gregory Alexander, Andrew Mark Bentley, Tim Felton, Tolga Turgut.

Manchester University, Manchester Royal Infirmary, United Kingdom. Andrew Martin, MB ChB, MRCP, FRCA, FFICM, CCT, Jonathan Bannard-Smith, Steve Benington, Patrick Hamilton, James Hanison, Nina Rendell, Anthony Wilson.

Royal Liverpool University Hospital, Liverpool, United Kingdom. Ingeborg Dorothea Maria Welters, MD, PhD, Oliver Hamilton, Brian Johnston, Suleman Mulla, Alicia Waite, Richard Wenstone.

United States

University of California, Davis Medical Center, Sacramento, California, United States. Timothy Albertson, MD, PhD, Stuart H. Cohen, M.D., Brian M. Morrissey, MD, Christian Sandrock, MD.

Baltimore VA Medical Center, Baltimore, Maryland, United States. Jacqueline Bork, MD, Jennifer Y. So, MD, Rohit Talwani, MD.

Maine Medical Center, Portland, Maine, United Stated. Kathryn Marie Brouillete, MD, CM, Sarah Marie Bray, MD, Raymond M Klein, MD, Katherine T. Liu, MD, Daniel A. Meyer, MD.

G.V.(Sonny) Montgomery Veterans Administration Medical Center, Jackson, Mississippi, United States. Mary Jane Burton, MD, Gwendolyn Adams-McAlpine, NP, Christian D. Weaver, MD.

Temple University Hospital, Philadelphia, Pennsylvania, United States. Gerard J. Criner, MD, James C. Brown, MD, Junad Mir Chowdhury, MD, Stephen E. Codella, MD, Parag B. Desai, MD, Gustavo Adolfo Fernandez Romero, MD, Rohit Gupta, MD, Fredric Jaffe, DO, Navjot Ariyana Kaur, MD, Samuel L. Krachman, DO, Albert James Mamary, MD, Nathaniel Marchetti, DO, Janpreet Mokha, MD, Oisin O'Corragain, MD, Maulin Patel, MD, Parth M. Rali, MD, Ekamjeet Singh Randhawa, MD, Daniel Alejandro Salerno, MD, MS, Kartik V. Shenoy, MD, Omar Sheriff, MD, Jeffrey I. Stewart, MD, Maria Elena Vega-Sanchez, MD, Steven R. Verga, MD, Ibraheem Fares Mohammad Yousef, MD, Matthew Zheng, MD.

Carilion Roanoke Memorial Hospital Carilion Clinic, Roanoke, Virginia, United States. Dorothy C. Garner, MD, Ekta N. Bansal, MD, Mariana Gomez De La Espriella, MD, Ruth Ndolo, RN, Fazili Tasaduq, MD, FACP, Jim Wong, MD.

The Lundquist Institute for Biomedical Innovation, Harbor UCLA Medical Center, Torrance, California, United States. Timothy J. Hatlen, MD, Eric S. Daar, MD.

Broward Health Medical Center, Florida, United States. Frank P. Hull, MD.

Mercy Health– Saint Vincent Medical Center, Toledo, Ohio, United States. Luis E. Jauregui-Peredo, MD, Salil Avasthi, MD, Tanyanyiwa W. Chinyadza, MD, Srinivas Katragadda, MD, James A. Tita, DO.

Renown Regional Medical Centre, Reno, Nevada, United States. Farah K. Madhani-Lovely, MD, Daniel Antwi-Amoabeng, MD, Rudy Tedja, DO.

Clement J Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin, United States. Sheran Mahatme, MD, Nathan D. Gundacker, MD.

Northwestern Medicine Central DuPage Hospital, Winfield, Illinois, United States. Luis A. Manrique, MD, Daniel Boyle, MD.

Regions Hospital, Saint Paul, Minnesota, United States. Charlene E. McEvoy, MD MPH, Omobosola O. Akinsete, MD, Charles A. Bruen, MD, Kealy Rae Ham, MD, Sarah Rebecca Peglow, MD.

Methodist Hospital, St. Louis Park, Minnesota, United States. Charlene E. McEvoy, MD MPH, Amanda Calvin, MD, Elizabeth Miller, MD.

Multicare Institute for Research & Innovation, Tacoma, Washington, United States. Patrick Scott Meehan, Jr., MD, Vinay Malhotra, MD.

University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States. Nikhil Kumar Meena, MD, Jose Diego Caceres, MD, Harmeen Goraya, MD, Larry Galdoc Johnson, MD.

Loma Linda University Medical Center, California, United States. H. Bryant Nguyen, MD, Terri Granillo, PA.

Memorial Hermann Hospital – Texas Medical Center, Texas, United States. Bela Patel, MD, Bindu Akkanti, MD, Luis Zeichner Ostrosky, MD.

Veterans Administration Western New York Healthcare System, New York, United States. Karin A. Provost, DO, PhD, Gregory Scott Fuhrer, MD, Jeffery M Mador, MD, Archana Mishra, MD.

Holy Cross Hospital, Silver Spring, Maryland, United States. Lee Edward Schwab, MD, Bernice Wiredu Aidoo, MD, Miriam Louise Cameron, MD, Ramani Reddy, MD.

Holy Cross Germantown Hospital, Germantown, Maryland, United States. Lee Edward Schwab, MD, Miriam Louise Cameron, MD, Farah Munnir Cheema, MD, Sameer B. Ismailjee, MD.

Pulmonary Associates of Mobile, Mobile, Alabama, United States. Allan F. Seibert, IV, MD, Michele L. Hemphill, RN, Daniel Joseph Pollman, MD.

Atrium Health, Charlotte, North Carolina, United States. Zainab Shahid, MD, Michael Sean Boger, MD, Yvonne Lynnette Carter, MD, Tedra Claytor, MD, Lisa E. Davidson, MD, Azeem Elahi, MD, Joseph P. Lang, MD, Michael K. Leonard, MD, Lewis Hall McCurdy, MD, Leigh Ann Medaris, MD, Tue H. Ngo, MD, Fred C. Papali, MD, CM, Christopher Polk, MD, Nestor Manuel Quezada, MD, Mindy M. Sampson, MD, DO, Jaspal Singh, MD, Kranthi K. Sitammagari, MD, Stephanie L. Strollo, MD, Brice Thomas Taylor, MD, Shelley S. Towery, RN, David Allan Weinrib, MD, Michael Zgoda, MD, Sara Zulfigar, MD.

North Florida South Georgia Veterans Health System, Gainesville, Florida, United States. Peruvemba S. Sriram, MD.

Doylestown Hospital, Doylestown, Pennsylvania, United States. Les A. Szekely, MD, Pinak Sumant Acharya, MD, Manuel Jose Jimenez-Serrano, MD, Kathy Tran-Gast, DO.

Supplementary Methods

Modified World Health Organisation (WHO) Ordinal Scale

1 = not hospitalised, no limitation of activity

2 = not hospitalised, limitation of activity

3 = hospitalised, no oxygen therapy

4 = hospitalised, low-flow oxygen by mask or nasal prongs

5 = hospitalised, high-flow oxygen (≥15 L/min), continuous positive airway pressure, bilevel positive airway pressure, non-invasive ventilation

6 = hospitalised, intubation and mechanical ventilation

7 = hospitalised, mechanical ventilation plus additional organ support

8 = death.

Blinding

An unblinded pharmacist dispensed the study intervention, ensuring no differences in labelling or time taken to dispense between the two interventions. Investigators who enrolled the patients, and the patients remained blinded to assigned study intervention.

Endpoints and assessments

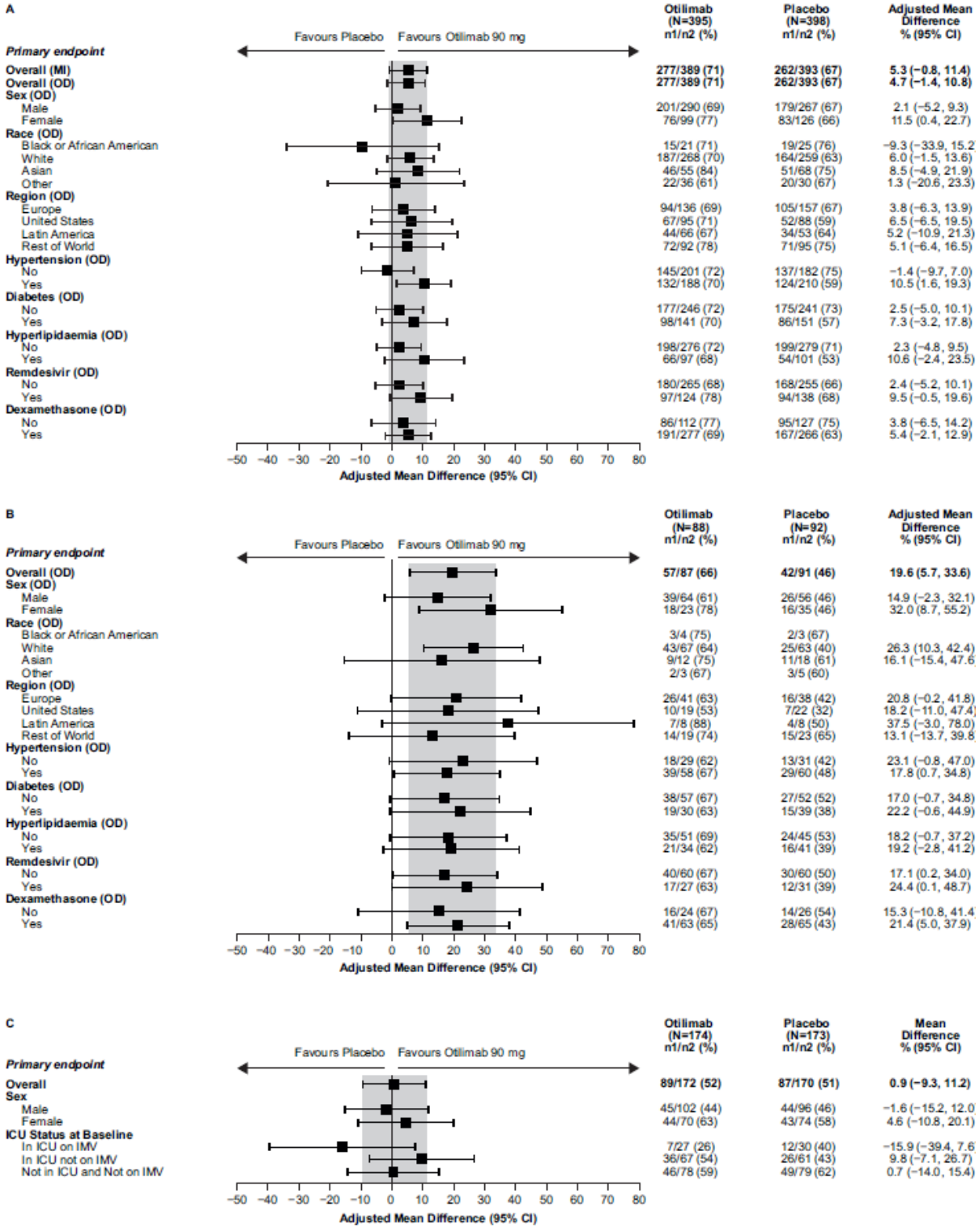
Exploratory endpoints (to Day 28, unless otherwise specified) included time to IMV (if not previously initiated); time to extubation; improvement, relative to baseline, in fraction of inspired oxygen (FiO_2) (estimated using the 3%-formula [1]); time to clinical status improvement of ≥2 categories, relative to baseline (to Day 60), PK parameters (to Day 14); exposure-response relationship for key efficacy, safety, and

PD biomarker endpoints; and change in markers of inflammation including, but not limited to, CRP, ferritin and inflammatory cytokines.

Pharmacokinetic (PK) and exposure-response analysis

A two-compartment PK model with first-order elimination from the central compartment with the covariate bodyweight on clearance and volume terms was developed using combined PK data from both parts and prior PK model information from 4 previous otilimab studies (EudraCT2007-007614-11, EudraCT2011-001809-27, [2, 3]). The model was used to derive the individual exposure metrics of area under the concentration-time curve (AUC) and maximum concentration (C_{max}) that were then used for exploratory exposure-response analysis for key efficacy, safety, and pharmacodynamic (PD) biomarker endpoints.

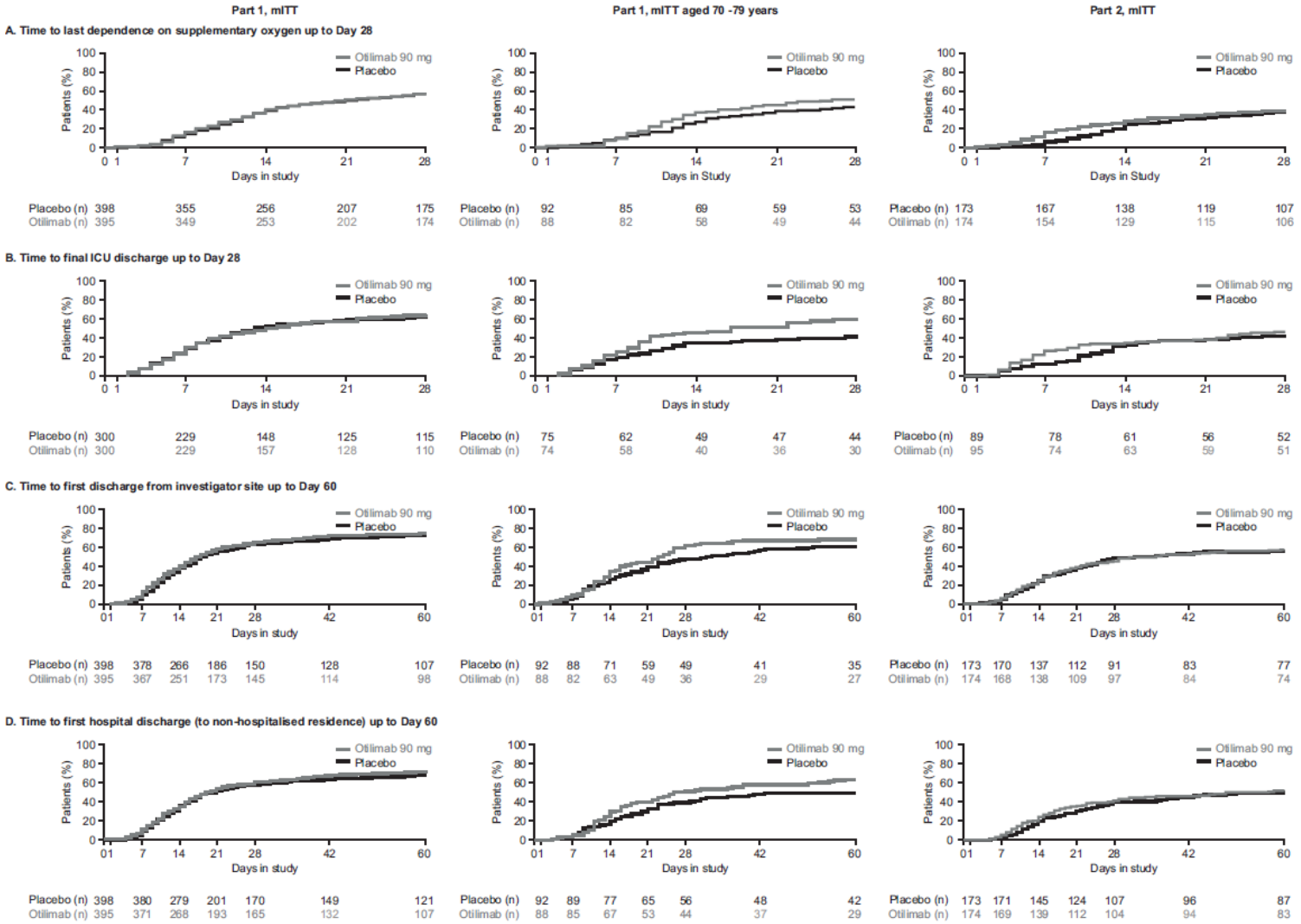
Figure S1. Patients alive and free of respiratory failure at Day 28 (primary endpoint) by baseline characteristic in Part 1 (A), Part 1 ≥70 years age subgroup (post hoc analysis; B), and Part 2 (C)

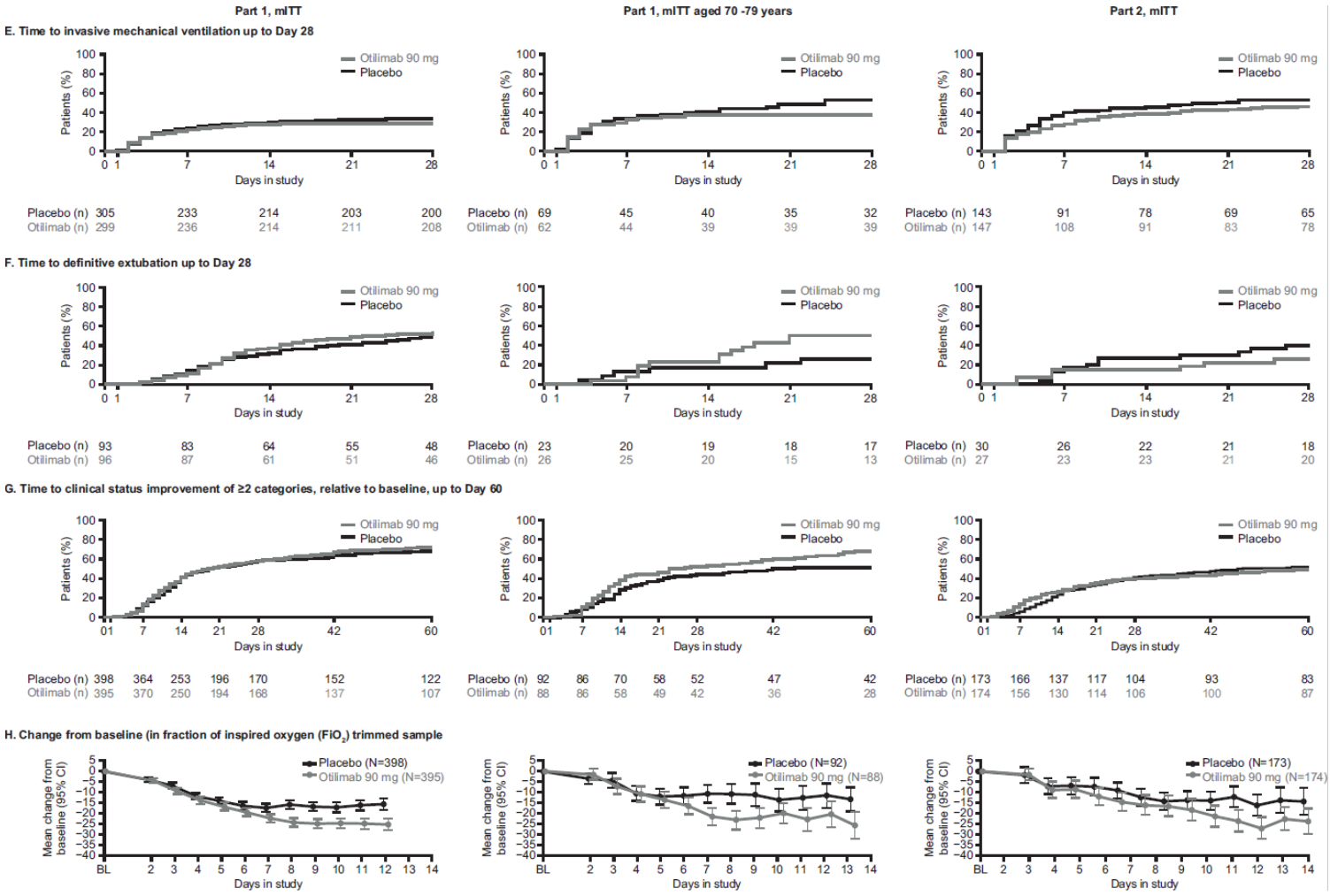


CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; MI, multiple imputation; OD, observed data.

Figure S2. Kaplan-Meier plots of time-to-event analyses

Secondary endpoints: Kaplan-Meier time to last dependence on supplementary oxygen up to Day 28 (A); Kaplan-Meier time to final ICU discharge up to Day 28 (B); Kaplan-Meier time to first discharge from investigator site up to Day 60 (C); Kaplan-Meier time to first hospital discharge (to non-hospitalised residence) up to Day 60 (D); exploratory endpoints: Kaplan-Meier time to invasive mechanical ventilation up to Day 28 (E); Kaplan-Meier time to definitive extubation up to Day 28 (F); Kaplan-Meier time to clinical status improvement of ≥2 categories, relative to baseline, up to Day 60 (G);mean change from baseline (95% CI) in fraction of inspired oxygen (FiO_2) trimmed sample (H) in the mITT population of Part 1, post hoc ≥70-year age group of Part 1, and in the mITT population of Part 2





BL, baseline; CI, confidence interval; ICU, intensive care unit; mITT, modified intent-to-treat.

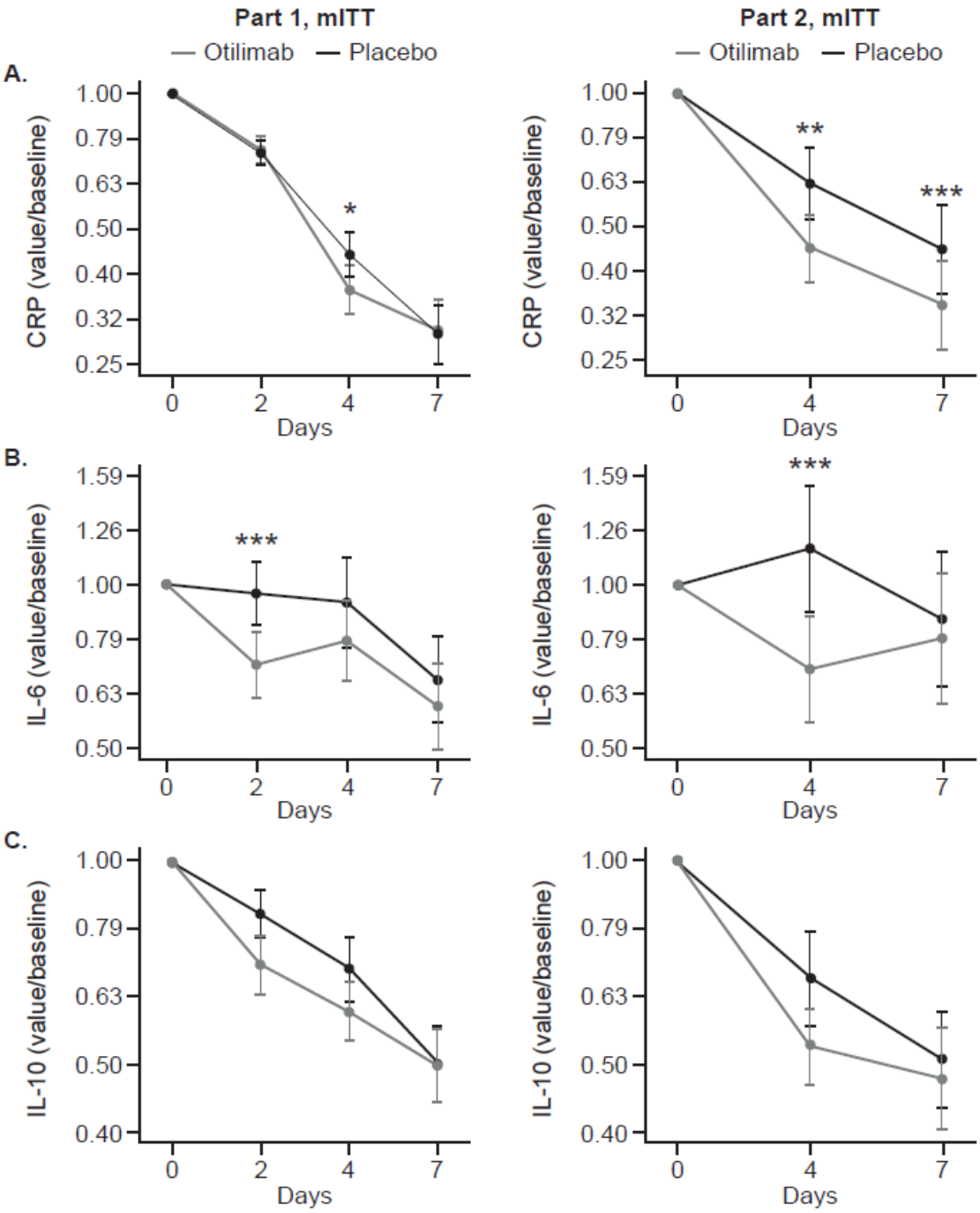
Table S1. Otilimab, free GM-CSF, and GM-CSF–otilimab complex concentrations

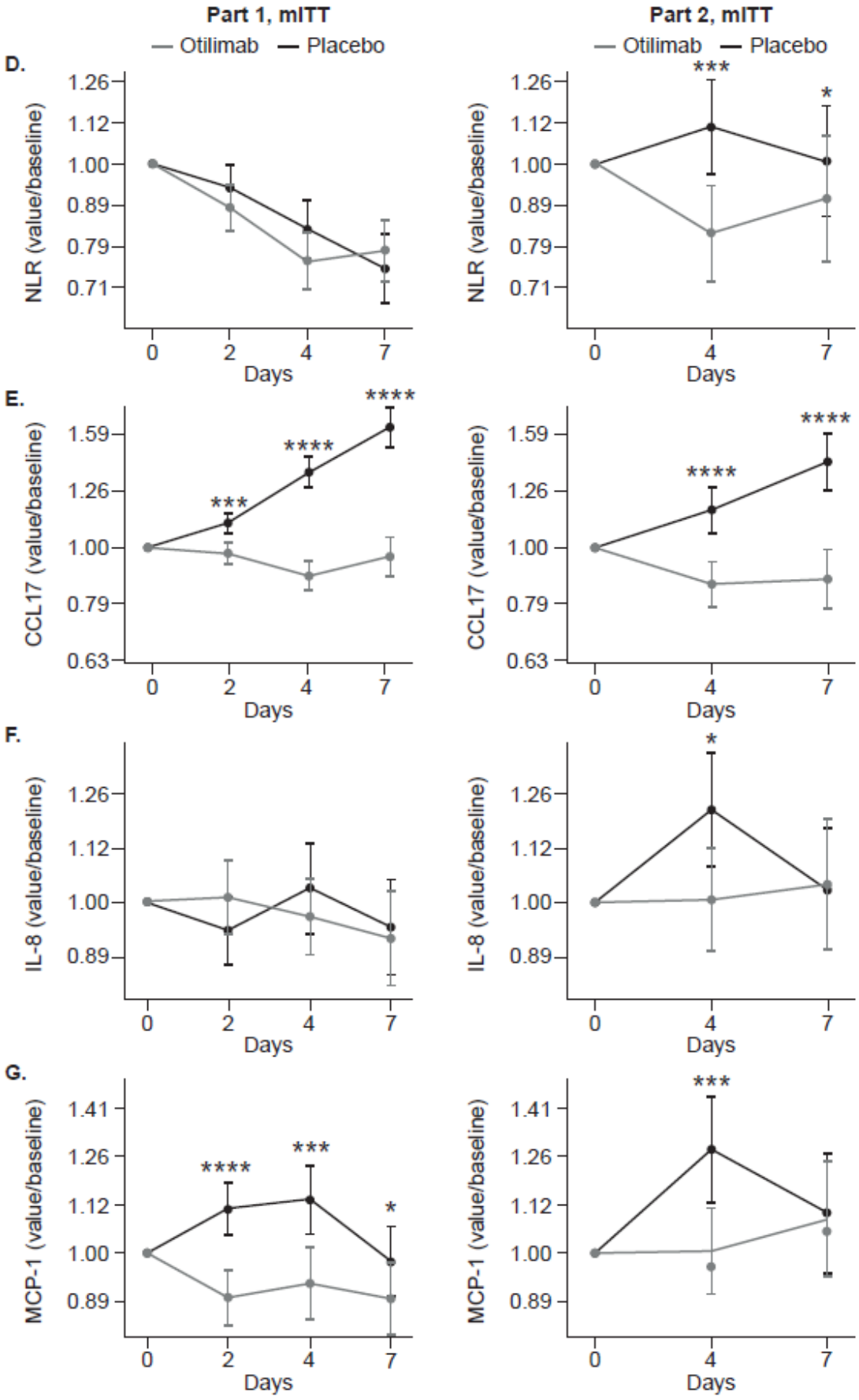
Variable	Part 1	Part 2
Otilimab serum concentration (ng/mL), median (min, max)		
Day 1	19600 (277, 584000)	20100 (339, 183000)
Day 2	12600 (226, 35300)	12700 (790, 35200)
Day 7	1840 (208, 17100)	1780 (394, 6930)
Day 14	336 (202, 2400)	314 (202, 1410)
Free GM-CSF concentration (pg/mL), median (min, max)		
Day 1	0.480 (0.0550, 9.70)	0.460 (0.0500, 13.0)
GM-CSF–otilimab complex concentration (pg/mL), median (min, max)		
Day 1	13.8 (5.81, 40.3)	11.7 (7.79, 20.8)
Day 2	24.7 (5.29, 953)	24.6 (6.15, 221)
Day 7	191 (6.29, 1290)	166 (7.96, 1540)
Day 14	54.6 (6.11, 599)	55.2 (7.36, 528)

GM-CSF, granulocyte-macrophage colony-stimulating factor.

Figure S3. Change from baseline in clinical biomarkers using linear mixed modelling

Fold change from baseline in CRP (A), IL-6 (B), IL-10 (C), neutrophil-to-lymphocyte ratio (D), CCL17 (E), IL-8 (F), and MCP-1 (G) in the mITT population of Part 1 and Part 2. Data presented as geometric mean with 95% CI derived from standard error (P*<0.05, ***P*<0.01, ****P*<0.001 and *****P*<0.0001, for otilimab versus placebo, by analysis of variance [ANOVA] F-test).**





CRP, C-reactive protein; IL, interleukin; MCP, macrophage chemotactic protein-1; mITT, modified intent-to-treat; NLR, neutrophil-to-lymphocyte ratio.

Figure S4. Otilimab concentration-time curves

Overlay of individual observed otilimab serum concentrations over time for the OSCAR pharmacokinetics population datasets for Part 1 and Part 2 in their respective overall (A) and age ≥70 years (B) subgroups.

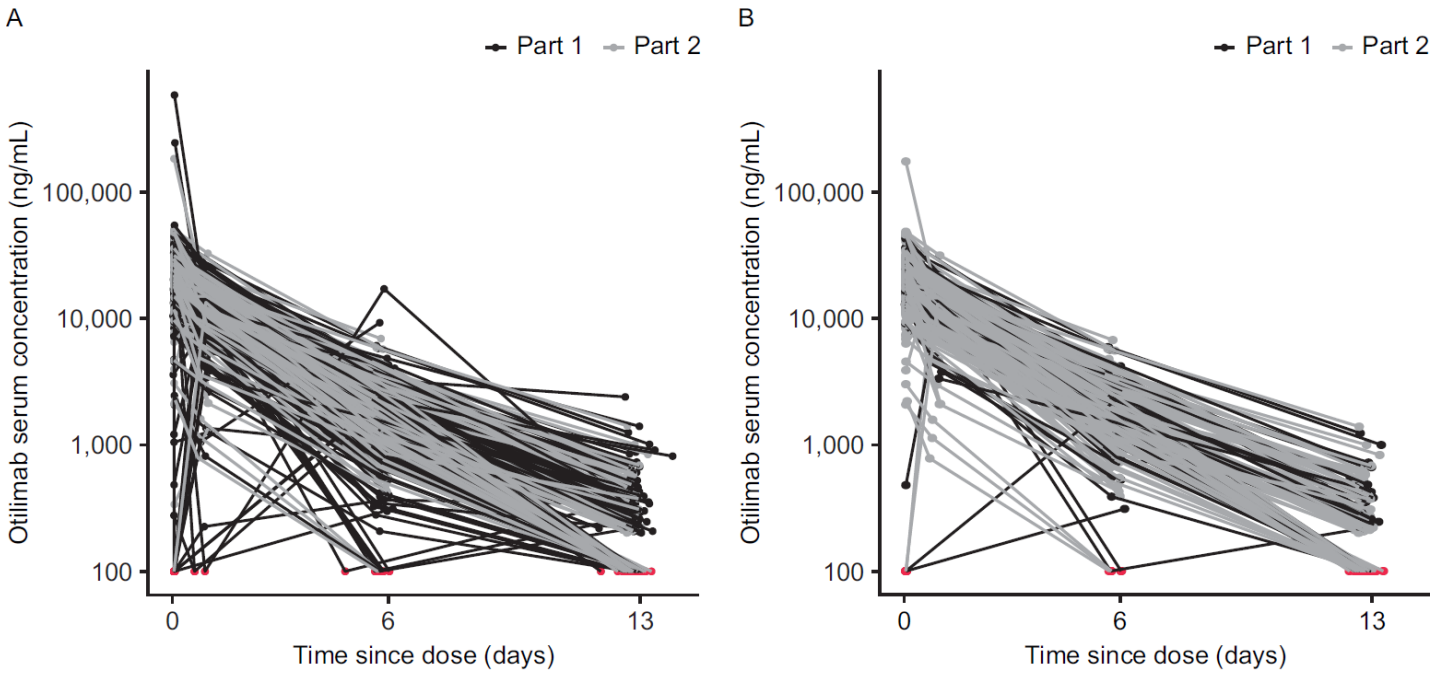
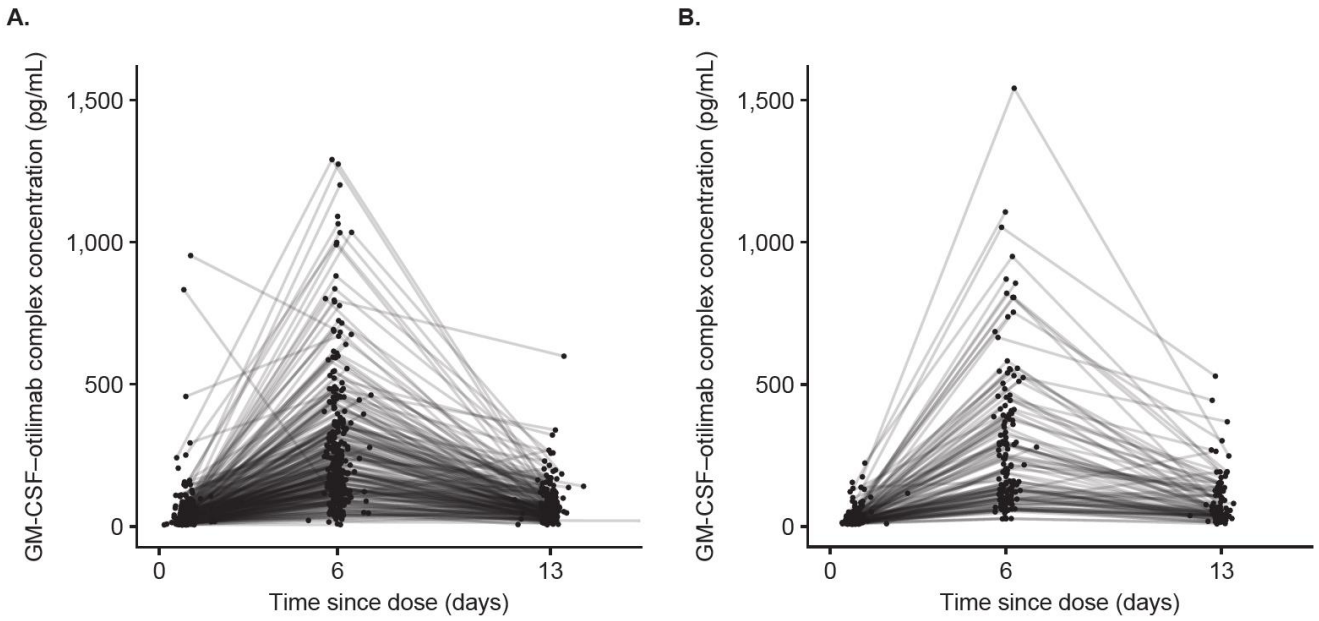


Figure S5. GM-CSF–otilimab complex concentration-time curve

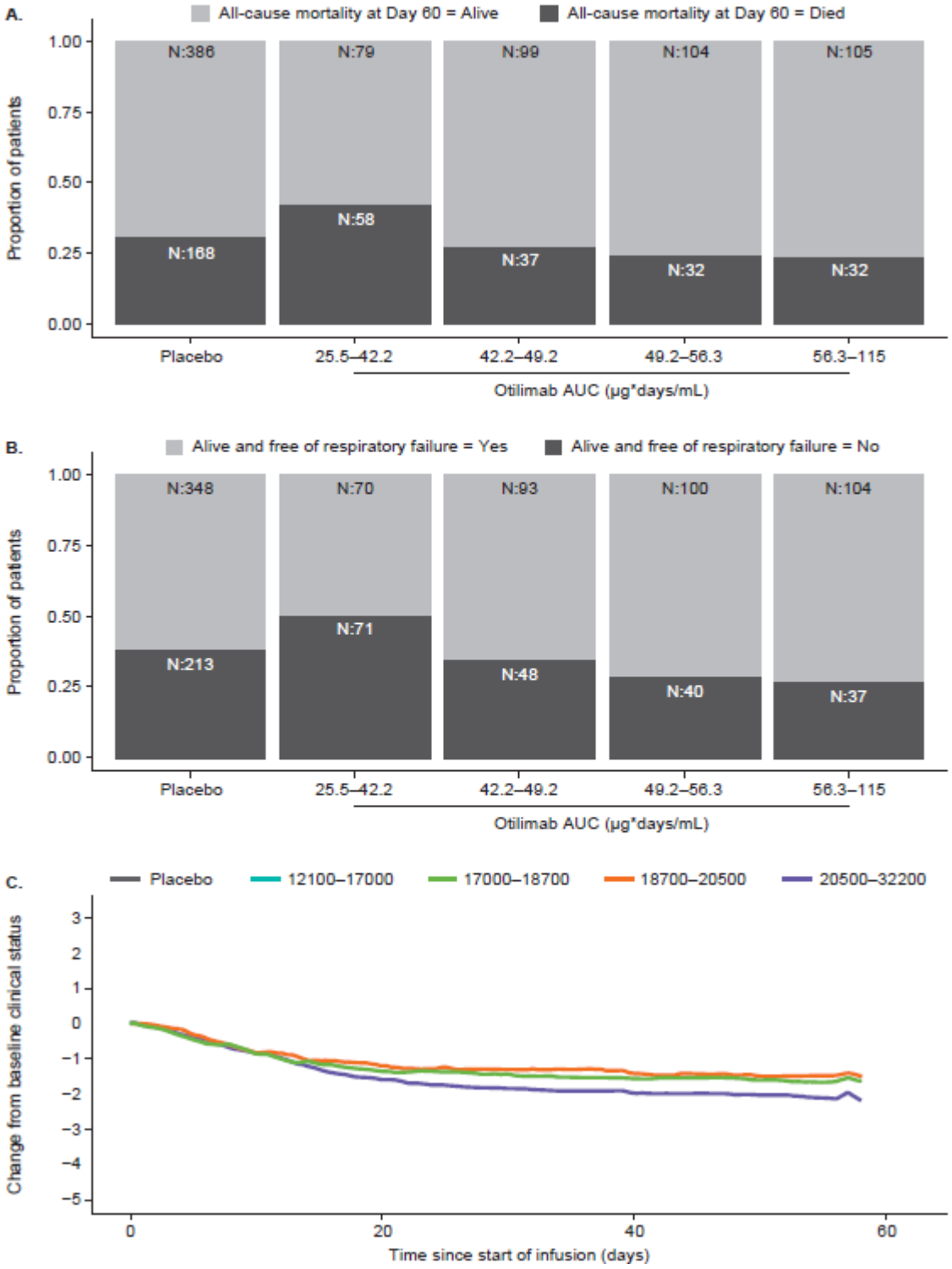
Overlay of individual observed GM-CSF–otilimab complex concentrations versus time after first dose for the COVID-19 patients in the otilimab target engagement analysis data set for Part 1 (A) and Part 2 (B).



GM-CSF, granulocyte-macrophage colony-stimulating factor.

Figure S6. Proportion of patients alive and free of respiratory failure at Day 28 (A) and all-cause mortality at Day 60 (B) versus the AUC percentile.

Mean change from baseline in clinical status over time grouped by C_{max} percentile (C). Percentiles: ≤25th; >25th to ≤50th; >50th to ≤75th; >75th to <Max.



References

1. Coudroy R, Frat JP, Girault C, et al. Reliability of methods to estimate the fraction of inspired oxygen in patients with acute respiratory failure breathing through non-rebreather reservoir bag oxygen mask. Thorax 2020; 75: 805-807.
2. Behrens F, Tak PP, Ostergaard M, et al. MOR103, a human monoclonal antibody to granulocyte-macrophage colony-stimulating factor, in the treatment of patients with moderate rheumatoid arthritis: results of a phase Ib/IIa randomised, double-blind, placebo-controlled, dose-escalation trial. Ann Rheum Dis 2015; 74: 1058-1064.
3. Constantinescu CS, Asher A, Fryze W, et al. Randomized phase 1b trial of MOR103, a human antibody to GM-CSF, in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2015; 2: e117.