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Early View

Original research article

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A randomised phase 2a study to investigate the effects of blocking IL-33 with tozorakimab in patients hospitalised with COVID-19: ACCORD-2

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Take home message (251/256): Tozorakimab was well tolerated, and post hoc analyses suggest that treatment effects may be enhanced in patients with severe disease and those with high baseline levels of serum IL-33/ST2. These effects will be investigated in a global phase 3 study.

Running title: Tozorakimab in patients hospitalised with COVID-19

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Abstract (248/250 words max)

Background Increased serum interleukin (IL)-33 predicts poor outcomes in patients hospitalised with coronavirus disease 2019 (COVID-19). We examined the efficacy and safety of tozorakimab, a monoclonal antibody that neutralises IL-33, in improving outcomes in ACCORD-2 (EudraCT: 2020-001736-95).

Methods ACCORD-2 was an open-label, phase 2a study in adults hospitalised with COVID-19. Patients were randomised 1:1 to tozorakimab 300 mg + standard of care [SoC] or SoC alone. The primary endpoint was time to clinical response (sustained clinical improvement of ≥2 points on the World Health Organization ordinal scale, discharge from hospital or fit for discharge) by day 29. Other endpoints included death or respiratory failure, mortality, intensive care unit (ICU) admissions by day 29 and safety. Serum IL-33/soluble ST2 (sST2) complex was measured by high sensitivity immunoassay.

Results Efficacy analyses included 97 patients (tozorakimab + SoC, n=53; SoC, n=44). Median time to clinical response did not differ between the tozorakimab and SoC arms (8.0 and 9.5 days, respectively [hazard ratio 0.96 (80% confidence interval [CI] 0.70–1.31), one-sided p=0.33]). Tozorakimab was well tolerated, and the odds ratio for risk of death or respiratory failure with treatment vs SoC was 0.55 ([80% CI 0.27–1.120], p=0.26), whilst the odds ratio was 0.31 (80% CI 0.09–1.06) in patents with high baseline serum IL-33/sST2.

Conclusions Overall, ACCORD-2 results suggest that tozorakimab could be a novel therapy for patients hospitalised with COVID-19, warranting further investigation in confirmatory phase 3 studies.

Introduction

Coronavirus disease 2019 (COVID-19) has rapidly developed into a global health threat [1]. The pathogenesis of severe COVID-19 is driven by complex immuno-inflammatory dysregulation [2, 3]. This dysregulation may lead to acute respiratory distress and multiorgan failure [3-6] approximately 7 days after the first symptoms [2].

Few approved therapeutic agents are currently available to treat severe COVID-19, and despite the impact of vaccination on reducing severe disease and mortality, there remains an urgent need for rapid development of efficacious interventions. Immunocompromised or unvaccinated individuals remain at risk of severe disease [7-11] and vaccinated individuals carry residual risk because vaccines are less than 100% effective and reduce in effectiveness over time owing to waning immunity and the emergence of variants [7-9]. Knowledge of prognostic biomarkers to identify patients at risk of poor outcomes, and predictive biomarkers to identify responders to therapeutic agents would aid the development of novel drugs [12].

Interleukin (IL)-33 is a broad-acting epithelial 'alarmin' cytokine constitutively expressed and stored in epithelial and endothelial cells [13], where it is rapidly released in response to cellular stress, tissue injury or infection [14]. Reduced IL-33 signals via serum stimulated-2 (ST2), whereas oxidised IL-33 signals via a complex of receptors for advanced glycation end-products and epidermal growth factor [15, 16]. ST2 is expressed in two isoforms, cell surface receptor ST2L and soluble ST2 (sST2), which is an endogenous antagonist of IL-33 activities [17, 18]. Excess release of IL-33 may drive dysregulated hyper-inflammation in severe acute respiratory syndrome coronavirus 2 infection [19]; IL-33 levels are increased in patients with COVID-19 and are associated with disease severity [20]. Tozorakimab is a high-affinity human immunoglobulin G1 monoclonal antibody that neutralises IL-33 [15], and has therapeutic potential to improve clinical outcomes in patients hospitalised with COVID-19.

ACCORD-2 is a randomised, adaptive-platform phase 2a study designed for the rapid assessment of multiple treatments added to standard of care (SoC) for patients hospitalised with COVID-19. The protocol of this study has been published previously [21]. The study was designed as a master protocol with candidate drugs evaluated using sub-protocols [21]. The aim of this sub-protocol presently discussed was to evaluate the efficacy and safety of tozorakimab in improving clinical outcomes in patients hospitalised with COVID-19.

Methods

Study participants

The study included patients aged 18 years or older, who were hospitalised with COVID-19 and met the clinical status of grade 3 (hospitalised – mild disease, no oxygen therapy), 4 (hospitalised – oxygen by mask or nasal prongs) or 5 (hospitalised – non-invasive ventilation or high-flow oxygen) of the World Health Organization Working Group on the Clinical Characteristics of COVID-19 nine-point ordinal scale (OS) 2020, as per the study protocol [21]. All patients provided written informed consent. Key exclusion criteria included a previous score of grade 6 or 7 on the OS, myocardial infarction within 3 months before the first dose of study treatment, unstable angina, a history of clinically significant arrhythmia, stage 4 chronic kidney disease or requiring dialysis. Exclusion criteria specific to the tozorakimab sub-protocol were patients with active tuberculosis, and those with a known family history of heart failure. Full inclusion and exclusion criteria are listed in the supplementary methods.

Study design

The randomised, open-label, seamless, adaptive, controlled, phase 2 study was conducted in over 15 centres in the UK. The study was initially planned as a two-part study: stage 1 being the pilot stage and stage 2 being the confirmatory stage. Stage 1 was planned to assess the following: preliminary safety and efficacy, optimal study endpoints and the number of patients to enrol in stage 2 of the study. Following changes in COVID-19 presentation, only the first part was conducted; the results of which are reported in this publication. The study was associated with the UK COVID-19 Antivirals and Therapeutics Taskforce, designed to evaluate potential treatments for COVID-19. Patients were recruited during two periods: 20 May 2020 to 24 July 2020 (period 1) and 8 December 2020 to 2 March 2021 (period 2). These periods coincided with COVID-19 waves that occurred in the UK and the first period occurred when no vaccinations were available. The B.1.1.7 virus, which was more virulent than previous COVID-19 variants [22], emerged during period 2. The study assessed the efficacy and safety of agents added to SoC *versus* SoC alone.

The study protocol was reviewed and approved by the UK Medicines and Healthcare Products Regulatory Agency (EudraCT: 2020-001736-95; registered 28 April 2020). Ethical approval was received from the relevant health research authority and research ethics committee. An independent data monitoring committee assessed safety throughout the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International

Council for Harmonisation (ICH) Good Clinical Practice Guidelines, and applicable local laws and regulations. The ACCORD-2 study was sponsored by University Hospital Southampton NHS Foundation Trust and funded by UK Research and Innovation.

Drug administration

Patients were randomised to receive either a single dose of tozorakimab 300 mg intravenously in addition to SoC (tozorakimab arm) or SoC alone (SoC arm). Tozorakimab was provided by AstraZeneca. Patients started treatment upon randomisation (day 1), within 24 hours of enrolment and screening (see supplementary methods for details). A second dose of tozorakimab 300 mg was administered on day 15 if the patient was receiving invasive mechanical ventilation. The tozorakimab dose rationale for patients with COVID-19 was based on results of a tozorakimab phase 1 study in healthy volunteers and patients with chronic obstructive pulmonary disease (COPD) [23, 24]. The SoC was based on appropriate guidelines in place at the time of each patient's participation, and consequently evolved over time. Agents administered as SoC are listed in the supplementary methods.

Outcomes

The primary endpoint was time from randomisation to clinical response, defined as sustained clinical improvement of at least 2 points on the OS, discharge from hospital or considered fit for discharge (0, 1 or 2 on the OS), whichever came first, by day 29. Sustained clinical improvement was defined as improvement without subsequent worsening before day 29. Patients who did not meet the above conditions by day 29 were censored at the day of their last OS assessment (*i.e.* either on day 29 or earlier), except for patients who died before day 29, who were censored at day 29.

Secondary endpoints assessed were death or respiratory failure (according to the OS) at day 29; survival (mortality at days 15, 29 and 60); proportion of patients not deteriorating according to the OS by 1, 2 or 3 points on days 15 and 29; duration of new invasive ventilation and duration of ventilation-free days; and duration of intensive care unit (ICU) stay and hospitalisation. Safety was also assessed as a secondary endpoint; please see supplementary methods for further details of safety assessments.

Exploratory biomarker analysis

The secondary outcome of risk of death or respiratory failure at day 29 was assessed by baseline levels of the serum biomarker IL-33/sST2 complex and by median baseline serum sST2. It was hypothesised that a high level of baseline IL-33/sST2 complex may be a potential predictive biomarker to identify tozorakimab responders. Increased serum sST2 level has

been shown to be a prognostic marker of poor outcomes in patients with COVID-19. [25] The level of serum IL-33/sST2 complex was measured by high-sensitivity immunoassay (S-plex, MSD, Rockville, MD, USA) [26]. Serum sST2 was measured using the Presage® sST2 immunoassay (Critical Diagnostics, San Diego, CA, USA).

Statistical analyses

The pre-specified significance threshold for assessing efficacy in this initial pilot stage of the study was a 10% one-sided level. This was considered appropriate for identifying potential signals of efficacy for further evaluation in the confirmatory stage. It was expected that 54 patients per arm would provide 80% power to detect a hazard ratio (HR) of 1.6 for the primary endpoint when comparing each candidate agent with SoC, assuming 70% of patients in the SoC arm would improve, be discharged from hospital or be considered fit for discharge at day 29.

The safety analysis set included all patients who received at least one dose of study medication and was used for presentation of baseline and safety data. The full analysis set, used for presentation of efficacy data, included all patients who received at least one dose of study medication and for whom at least one post-baseline OS score was available.

Primary endpoint data were analysed using a log-rank test. The HR and associated two-sided 80% confidence interval (CI) representing the overall treatment effect were estimated using the stratified Cox proportional hazards regression model, containing treatment, age and baseline severity grade as covariates. The median, quartiles and two-sided 80% CIs were estimated using the Kaplan–Meier method. For secondary endpoints, proportions were analysed using the Cochran–Mantel–Haenszel test (stratified for baseline severity), with odds ratio (OR) and 80% Wald CIs calculated using logistic regression, adjusting for age and baseline severity grade as covariates.

Outcomes were presented for the study overall; however, owing to differences in COVID-19 variants and changes in SoC during the study, additional *post hoc* exploratory analyses of key endpoints were reported for patients recruited during period 2 only. The exploratory subgroup analyses were conducted on the following biomarkers with cut-offs determined by the overall median value at baseline: IL-33/sST2 complex (<30.15 U/mL or ≥30.15 U/mL) and sST2 (<114.6 ng/mL or ≥114.6 ng/mL).

All analyses were reported according to the ICH E9 guidelines on statistical principles in clinical trials. Further methodology details are available in the supplementary methods.

Results

Patient characteristics

Overall, 105 patients were enrolled in the tozorakimab sub-protocol and 103 were randomised. Five patients were excluded from the safety analysis set (n=98; tozorakimab + SoC, n=54; SoC alone, n=44) (figure 1). Most patients were recruited during period 2 (tozorakimab + SoC, n=49; SoC alone, n=32). One patient in the tozorakimab arm did not have a post-dose OS assessment and was excluded from the full analysis set (n=97) but included in the safety analysis set (n=98).

Baseline demographics and patient characteristics of the overall cohort and of those recruited during period 2 are reported in table 1 and supplementary table 1, respectively. In the overall cohort, the mean (standard deviation [SD]) age was 55.4 (12.5) and 58.0 (13.9) years in the tozorakimab and SoC arms, respectively (table 1). Patients in the tozorakimab arm had a higher mean (SD) baseline National Early Warning Score (NEWS)2 score than those in the SoC arm (4.8 [2.2] *vs* 4.0 [2.1]; table 1). More patients in the tozorakimab arm than in the SoC arm had at least two comorbidities (38.9% *vs* 29.5%, respectively; table 1). Most patients had a grade 4 clinical status (77.8% and 75.0% in the tozorakimab and SoC arms, respectively). One patient in the SoC arm (2.3%) was vaccinated at baseline; additional patients were vaccinated during the study (n=10 [18.5%] and n=3 [6.8%] in the tozorakimab and SoC arms, respectively).

Primary outcome

The median (interquartile range) time to clinical response by day 29 did not differ between the two arms (tozorakimab arm, 8.0 [5.0–22.0] days; SoC arm, 9.5 [4.0–not estimated] days; HR: 0.96 [80% CI 0.70–1.31]; p=0.33) (figure 2 and table 2).

Secondary outcomes

Twenty patients died or were in respiratory failure by day 29; nine (17.0%) in the tozorakimab arm and 11 (25.0%) in the SoC arm (figure 3a). The OR for risk of death or respiratory failure at day 29 with tozorakimab compared with SoC was 0.55 (80% CI 0.27–1.12; p=0.26) (figure 3a).

Mortality at all time points for the tozorakimab and SoC arms is summarised in supplementary table 2; at day 29, a mortality of 11.3% *versus* 13.6% was observed, respectively (OR 0.70 [80% CI 0.29–1.71; p=0.62]) (figure 3b).

The proportion of patients who did not deteriorate, as measured by OS score, in the tozorakimab and SoC arms for all time points is presented in supplementary table 3. The proportion of patients discharged from hospital was 83.0% [n=44] in the tozorakimab arm *versus* 79.5% [n=35] in the SoC arm (HR 0.92 [80% CI 0.68–1.25; p=0.79]) (supplementary table 4). The mean (SD) proportion of days on ventilation for patients in the tozorakimab and SoC arms was 7.7% (21.3%) *versus* 12.4% (26.0%), respectively (supplementary table 5). By day 29, nine patients (17.0%) in the tozorakimab arm and 11 (25.6%) patients in the SoC arm had been admitted to ICU (OR 0.52 [80% CI 0.26–1.04]) (figure 3c).

Safety

Treatment-emergent adverse events (TEAEs) of any grade occurred in 39 patients (72.2%) in the tozorakimab arm and 26 patients (59.1%) in the SoC arm (table 3). The most common TEAE categories (reported in >15% of patients in both groups) in the tozorakimab and SoC arms, respectively, were infections and infestations (20.4% and 25.0%), respiratory, thoracic and mediastinal disorders (22.2% and 20.5%) and gastrointestinal disorders (20.4% and 15.9%).

Serious TEAEs of any grade occurred in 14 patients (25.9%) in the tozorakimab arm and 10 patients (22.7%) in the SoC arm. The most common serious TEAEs in the tozorakimab and SoC arms, respectively, were pulmonary embolism (3.7% and 6.8%), dyspnoea (5.6% and 0.0%) and sepsis (3.7% and 2.3%). TEAEs leading to death occurred in two patients (3.7%) in the tozorakimab arm and four patients (9.1%) in the SoC arm (table 3).

Post hoc analyses

In the subgroup of patients recruited in period 2, there was a statistically significant reduction in the risk of death or respiratory failure at day 29 in those treated with tozorakimab compared with SoC (n/N=8/49 [16.3%] *vs* n/N=10/32 [31.3%]; OR 0.31 [80% CI 0.14–0.70]) (figure 3a). In this subgroup, a mortality of 12.2% *versus* 18.8%, in the tozorakimab and SoC arms, respectively, was observed by day 29 (OR 0.42 [80% CI 0.16–1.08]) (figure 3b). The risk of

ICU admission was also significantly reduced in the tozorakimab arm compared with the SoC arm in this subgroup (OR 0.31 [80% CI 0.14–0.67]) (figure 3c).

Exploratory biomarker analyses

The secondary outcome of risk of death or respiratory failure at day 29 was assessed by baseline levels of the serum biomarker IL-33/sST2 complex. In this *post hoc* exploratory analysis, patients were divided into two groups based on the median baseline level of IL-33/sST2 (<30.15 U/mL and ≥30.15 U/mL).

A total of n=41 patients had IL-33/sST2 levels below 30.15 U/mL, n=25 in the tozorakimab arm and n=16 in the SoC arm. Among these patients, n=5 (20.0%) in the tozorakimab arm and n=4 (25.0%) in the SoC arm had experienced death or respiratory failure by day 29. There was no difference in the risk of death or respiratory failure between the treatment arms in this subgroup (OR 1.01 [80% CI 0.33–3.10]) (figure 4).

A total of n=41 patients had IL-33/sST2 of at least 30.15 U/mL, n=21 in the tozorakimab arm and n=20 in the SoC arm. Among these patients, n=3 (14.3%) in the tozorakimab arm and n=7 (35.0%) in the SoC arm had experienced death or respiratory failure by day 29. The OR for risk of death or respiratory failure at day 29 with tozorakimab compared with SoC was 0.31 [80% CI 0.09–1.06]) (figure 4).

Risk of death or respiratory failure at day 29 was also assessed using median baseline serum sST2, with the median level (114.6 ng/mL) used as a cut-off point. The OR for risk of death or respiratory failure at day 29 with tozorakimab compared with SoC in the group of patients with below baseline median serum sST2 level was 0.62 [80% CI 0.15–2.58]), and 0.44 [80% CI 0.17–1.10]) in those with sST2 at or above the median level (supplementary figure 1).

Discussion

In this study, the primary endpoint (time to clinical response) was similar between the tozorakimab and SoC arms. Although, the addition of tozorakimab to SoC in patients hospitalised with COVID-19 led to no significant overall improvement in clinical measures, tozorakimab treatment numerically reduced the risk of death, respiratory failure and ICU

admission, compared with SoC alone. Notably, post hoc analysis suggests that tozorakimab treatment may have enhanced effects in a subgroup of patients with higher baseline levels of serum IL-33/ST2.

In this study, the recruitment of patients occurred during two periods, with most patients enrolled in period 2. Notably, during period 2 there were statistically significant reductions with tozorakimab *versus* SoC alone in the proportion of patients who died or were in respiratory failure and the proportion of patients admitted to an ICU. Period 1 occurred before the emergence of the B.1.1.7 virus, which was more virulent than previous COVID-19 variants [22]. Therefore, the severity of COVID-19 in patients enrolled during period 1 may not reflect the disease severity of those currently being admitted to hospital with COVID-19 (i.e. those at high risk of severe disease or immunocompromised individuals). For example, during period 1 there were no deaths, two patients presented with respiratory failure and only two ICU admissions occurred. Additionally, dexamethasone was included as the SoC in period 2, whereas period 1 mainly occurred before the use of dexamethasone. Therefore, data from period 2 are likely to be more relevant to current clinical practice than period 1. Overall, these results highlight the possibility that tozorakimab could be an effective therapy for patients hospitalised with COVID-19 at risk of acute respiratory failure or death, even in conjunction with dexamethasone therapy.

Targeting the IL-33/ST2 axis has shown potential for controlling excessive lung inflammation [27]; several phase 2 trials are investigating anti-ST2 and anti-IL-33 antibodies as therapies for other inflammatory diseases, such as COPD (NCT03546907; NCT03615040) and asthma (NCT03207243) [28]. Increased understanding of key mechanisms that drive poor outcomes in patients with COVID-19 has facilitated development of potential therapeutic strategies targeting the aberrant host hyper-inflammatory response [3, 29, 30]. IL-33 represents an attractive therapeutic target for COVID-19 because increased IL-33 levels might facilitate excess lung inflammation in patients hospitalised with COVID-19, and serum IL-33 levels correlate with poor clinical outcomes [31, 32].

Identification of precision medicine biomarkers may help to stratify patients to specific treatments that improve patient outcomes in COVID-19. In this study, exploratory biomarker analysis indicated that tozorakimab may have greater benefit in patients with elevated baseline levels of the IL-33/sST2 complex. We hypothesise that higher levels of circulating IL-33/sST2 complex reflects increased release of IL-33 in the airway and tozorakimab, by neutralising IL-33, will have greater benefit in this population. Consistent with this hypothesis, patients with

high levels of sST2 did not preferentially benefit from tozorakimab. However, further studies of the interplay of IL-33 and sST2 and the mechanism of tozorakimab in patients with COVID-19 are required.

Data from this study confirmed that tozorakimab was well tolerated in patients hospitalised with COVID-19. A higher proportion of patients in the tozorakimab arm experienced TEAEs than in the SoC arm; however, patients receiving active treatment in an open-label study compared with a blinded study may report a greater number of adverse events than those receiving SoC [33]. Of note, the proportion of patients with serious TEAEs was similar in both groups. Therefore, no safety findings from this study preclude further development of tozorakimab.

The health and economic impact of COVID-19 has been substantial [34] and a treatment that reduces mortality could save a significant number of lives and reduce the burden on healthcare systems. Dexamethasone has been shown to reduce mortality in patients with COVID-19 needing oxygen and ventilation by 18% and 36%, respectively [35]. In our study, treatment effects were observed in patients with severe disease and those with high baseline levels of serum IL-33/sST2 treated with both tozorakimab and SoC versus SoC alone. Consequently, tozorakimab could reduce mortality more than SoC alone, further alleviating the burden on healthcare systems.

Limitations of this study include the small sample size, particularly in subgroup analyses. The target sample size (≥54 patients per arm) was not reached due to recruitment challenges related to the rapidly changing environment of the COVID-19 pandemic. This led to a pause in recruitment after the end of the first UK COVID-19 wave. Conducting a study in an intense hospital environment meant that complete baseline data were not always available. Patients in the tozorakimab arm had a higher mean baseline NEWS2 score and a greater number of comorbidities than those in the SoC arm, suggesting that they had a worse prognosis. SoC changed during the study; the use of dexamethasone and tocilizumab was more widespread in period 2. Thus, the current SoC received by patients hospitalised with COVID-19 may differ from the SoC used in this study, which may limit the generalisability of the results. Furthermore, the emergence of COVID-19 variants during the study, which was conducted before widespread vaccination, should be considered when interpreting these results. In line with this, most patients who were included in the study were unvaccinated; owing to the subsequent vaccination programme in the UK, patients who are hospitalised with COVID-19 in current practice are likely to have increased immunity compared with the patients who were

assessed during this study. Finally, the sensitivity of the primary endpoint was limited because some patients recovered quickly from COVID-19, which may diminish the actual benefit observed in those with severe outcomes.

Conclusions

Results from this study demonstrated that tozorakimab was well tolerated. The primary endpoint was similar between tozorakimab and SoC arms, and tozorakimab showed no significant effect in reducing the risk of respiratory failure and death, or in reducing ICU admissions, compared with SoC overall. However, findings that the treatment effect of tozorakimab may be enhanced in a subgroup of patients recruited during a period associated with more severe disease and in those with high baseline serum IL-33/sST2 complex levels, warrant further investigation. A global phase 3 study is underway to assess the efficacy of tozorakimab in patients hospitalised with respiratory viral infection (TILIA: NCT05624450).

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Data sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: T. Wilkinson, D. Singh, C. Page, M. Carroll, L.-P. Ho. and G. Griffiths designed the study. T. Wilkinson, A. De Soyza, M. Carroll, J.D. Chalmers, M.G. Crooks, M. Shankar Hari, A. Horsley, B. Lara, B. Mishra, J. Raw, D. Saralaya, S. Siddiqui, A. Ustianowski, A. Woodcock and D. Singh contributed to data collection. T. Wilkinson, C. Page, M. Carroll, A. De Soyza, J.D. Chalmers, M.G. Crooks, M. Shankar Hari, A. Horsley, B. Lara, B. Mishra, J. Raw, D. Saralaya, S. Siddiqui, A. Ustianowski, A. Woodcock and D. Singh accessed and verified the underlying raw data in the study. T. Wilkinson, D. Singh, C. Page, M. Carroll, G. Griffiths, A. De Soyza, J.D. Chalmers, M.G. Crooks, M. Shankar Hari, A. Horsley, B. Lara, B. Mishra, J. Raw, S. Siddiqui, A. Ustianowski, A. Woodcock, D. Saralaya, H. Pandya, R. Moate, F. Reid, C. Kell, I.C. Scott and N. van Zuydam analysed and interpreted the data. All authors contributed to writing the article and approval of the final version.

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Figures and tables

TABLE 1 Baseline demographics and patient characteristics

Demographic/characteristic	Tozorakimab + SoC (n=54)	SoC (n=44)
Age, years, mean (SD)	55.4 (12.5)	58.0 (13.9)
Age ≥70 years	8 (14.8)	11 (25.0)
Sex, male	37 (68.5)	29 (65.9)
Body mass index, kg/m^2, mean (SD)	32.6 (8.1)	33.3 (8.5)
Smoking status		
Former	26 (48.1)	16 (37.2)
Current	2 (3.7)	0 (0.0)
Time since onset of symptoms		
<12 days	38 (70.4)	37 (84.1)
≥12 days	16 (29.6)	7 (15.9)
Derived baseline WHO OS score		
Grade 3	1 (1.9)	3 (6.8)
Grade 4	42 (77.8)	33 (75.0)
Grade 5	11 (20.4)	8 (18.2)
NEWS2 score, mean (SD)	4.8 (2.2)	4.0 (2.1)
Clinical frailty score at baseline		
Very fit	8 (14.8)	4 (9.1)
Well	22 (40.7)	16 (36.4)
Managing well	8 (14.8)	6 (13.6)
Vulnerable	6 (11.1)	5 (11.4)
Mildly frail	3 (5.6)	4 (9.1)
Moderately frail	7 (13.0)	9 (20.5)
Comorbidities at baseline[a]		
≥1	34 (63.0)	25 (56.8)
≥2	21 (38.9)	13 (29.5)
Comorbidity categories[a]		
Heart disease	5 (9.3)	6 (13.6)
Diabetes	22 (40.7)	13 (29.5)
Chronic lung disease	7 (13.0)	4 (9.1)
Chronic liver disease	1 (1.9)	0 (0.0)
Asthma	8 (14.8)	7 (15.9)
HIV	0 (0.0)	0 (0.0)
Tuberculosis	0 (0.0)	1 (2.3)
Cancer[b]	5 (9.6)	1 (2.4)
Hypertension[b]	15 (28.8)	13 (31.7)
Remdesivir at baseline[b]	34 (65.4)	25 (61.0)
Dexamethasone at baseline[b]	52 (100.0)	37 (90.2)

Supplemental oxygen at baseline	53 (98.1)	41 (93.2)
Received COVID-19 vaccine during the study	13 (24.1)	4 (9.1)

Data are presented as n (%) unless stated otherwise. [a]Percent values are based on the safety analysis set. [b]Percent values are based on 52 patients receiving tozorakimab and 41 patients receiving SoC. COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; NEWS: National Early Warning Score; OS: ordinal scale; SD: standard deviation; SoC: standard of care; WHO: World Health Organization.

TABLE 2 Primary endpoint: time to sustained clinical response

	Tozorakimab + SoC (N=53)	**SoC (N=44)**
Overall		
Patients with a sustained clinical response, n (%)	42 (79.2)	32 (72.7)
Censored, n (%)	11 (20.8)	12 (27.3)
Time to response, days, median (IQR)	8.0 (5.0–22.0)	9.5 (4.0–NE)
HR (80% CI), p value	0.96 (0.70–1.31), 0.33	-
	Tozorakimab + SoC (N=49)	**SoC (N=32)**
Period 2 only[a]		
Patients with a sustained clinical response, n (%)	39 (79.6)	22 (68.8)
Censored, n (%)	10 (20.4)	10 (31.3)
Time to response, days, median (IQR)	8.0 (5.0–22.0)	8.5 (54.5–NE)
HR (80% CI)	1.09 (0.77–1.54)	-

[a]Data for period 1 were not analysed separately owing to the very small proportion of patients recruited in period 1. CI: confidence interval; HR: hazard ratio; IQR: interquartile range; NE: not estimated; SoC: standard of care.

TABLE 3 TEAEs and serious TEAEs in the safety analysis set.

	Tozorakimab + SoC (N=54)	**SoC (N=44)**
TEAEs	39 (72.2)	26 (59.1)
System organ class		
Infections and infestations	11 (20.4)	11 (25.0)
Respiratory, thoracic and mediastinal disorders	12 (22.2)	9 (20.5)
Gastrointestinal disorders	11 (20.4)	7 (15.9)
Investigations	11 (20.4)	4 (9.1)
Nervous system disorders	5 (9.3)	8 (18.2)
Cardiac disorders	7 (13.0)	5 (11.4)
General disorders and administration site conditions	2 (3.7)	8 (18.2)
Metabolism and nutrition disorders	4 (7.4)	6 (13.6)
Psychiatric disorders	4 (7.4)	5 (11.4)
Skin and subcutaneous tissue disorders	5 (9.3)	3 (6.8)
Musculoskeletal and connective tissue disorders	4 (7.4)	4 (9.1)
Renal and urinary disorders	5 (9.3)	1 (2.3)
Preferred terms occurring in three or more patients in either arm		
Pulmonary embolism	3 (5.6)	5 (11.4)
Subcutaneous emphysema	0	3 (6.8)
Atrial fibrillation	2 (3.7)	4 (9.1)
Delirium	2 (3.7)	3 (6.8)
Dyspnoea	4 (7.4)	2 (4.5)
Epistaxis	5 (9.3)	0 (0.0)
Oral candidiasis	1 (1.9)	4 (9.1)
Constipation	4 (7.4)	0 (0.0)
Diarrhoea	1 (1.9)	3 (6.8)
Fall	3 (5.6)	1 (2.3)
Pneumonia	1 (1.9)	3 (6.8)
Alanine aminotransferase increased	3 (5.6)	0 (0.0)
Serious TEAEs occurring in two or more patients in either arm		
Patients with serious TEAEs	14 (25.9)	10 (22.7)
Pulmonary embolism	2 (3.7)	3 (6.8)

Dyspnoea	3 (5.6)	0 (0.0)
Sepsis	2 (3.7)	1 (2.3)
Acute myocardial infarction	2 (3.7)	0 (0.0)
COVID-19	2 (3.7)	0 (0.0)
Pneumonia	1 (1.9)	1 (2.3)
TEAEs[leading to death		
Patients with TEAEs leading to death	2 (3.7)	4 (9.1)
Acute respiratory distress syndrome	0 (0.0)	1 (2.3)
Blood culture positive	0 (0.0)	1 (2.3)
Carotid artery occlusion	0 (0.0)	1 (2.3)
Catheter site haemorrhage	1 (1.9)	0 (0.0)
Cerebral artery occlusion	0 (0.0)	1 (2.3)
Cerebral haemorrhage	1 (1.9)	0 (0.0)
Cerebral infarction	0 (0.0)	1 (2.3)
General physical health deterioration	0 (0.0)	1 (2.3)
Klebsiella infection	1 (1.9)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	1 (2.3)
Pulmonary embolism	0 (0.0)	1 (2.3)
Sepsis	1 (1.9)	0 (0.0)
Superinfection bacterial	0 (0.0)	1 (2.3)

Data are given as n (%). COVID-19: coronavirus disease 2019; SoC: standard of care; TEAE: treatment-emergent adverse event.

FIGURE 1 Trial profile.

FAS: full analysis set; SAS: safety analysis set; SoC: standard of care.

FIGURE 2 Kaplan–Meier analysis of time to sustained clinical response by day 29.

Kaplan–Meier curves were compared using a stratified log-rank test. SoC: standard of care.

FIGURE 3 Secondary outcomes – overall and by period 2: a) death or respiratory failure, b) mortality by day 29 and c) ICU admissions by day 29.

*p<0.1 (one-sided). Note: in panel c, one patient in the SoC group was excluded from the analysis because this individual was already in an ICU at the time of randomisation. Percentages are out of the number of patients included in the analysis. ORs (logistic regression model adjusted for age and baseline severity) are given with 80% CIs. CI: confidence interval; ICU: intensive care unit; OR: odds ratio; SoC: standard of care.

FIGURE 4 Death or respiratory failure at day 29 by baseline level of serum IL-33/sST2 complex.

Some patients had missing biomarker values at baseline. The cut-off is the median baseline IL-33/sST2 complex value. ORs were calculated from a logistic regression model adjusting for age and baseline severity. CI: confidence interval; IL: interleukin; OR: odds ratio; SoC: standard of care; sST2: soluble ST2.

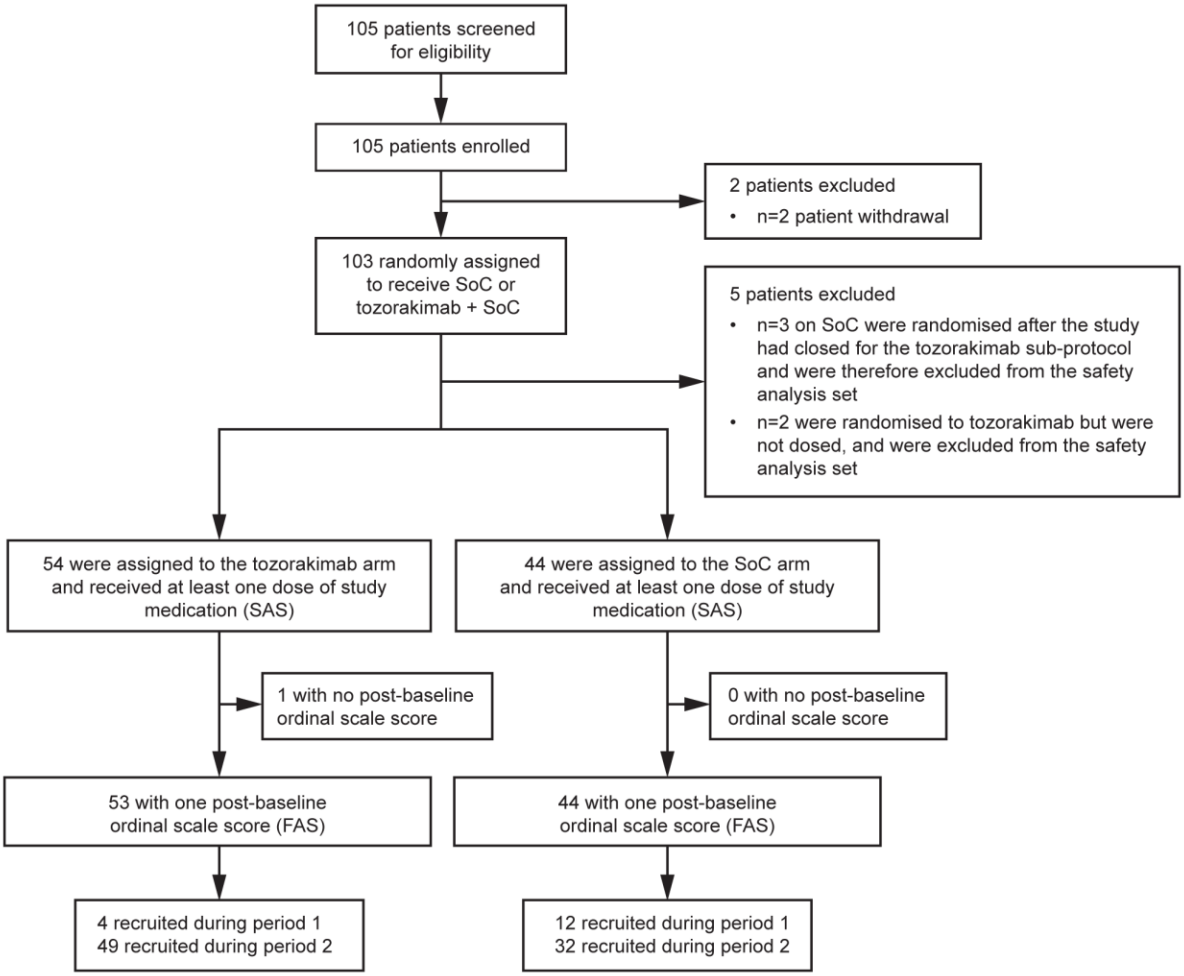

105 patients screened for eligibility
105 patients enrolled
2 patients excluded
• n=2 patient withdrawal
103 randomly assigned to receive SoC or tozorakimab + SoC
5 patients excluded
• n=3 on SoC were randomised after the study had closed for the tozorakimab sub-protocol and were therefore excluded from the safety analysis set
• n=2 were randomised to tozorakimab but were not dosed, and were excluded from the safety analysis set
54 were assigned to the tozorakimab arm and received at least one dose of study medication (SAS)
44 were assigned to the SoC arm and received at least one dose of study medication (SAS)
1 with no post-baseline ordinal scale score
0 with no post-baseline ordinal scale score
53 with one post-baseline ordinal scale score (FAS)
44 with one post-baseline ordinal scale score (FAS)
4 recruited during period 1
49 recruited during period 2
12 recruited during period 1
32 recruited during period 2

Figure 1

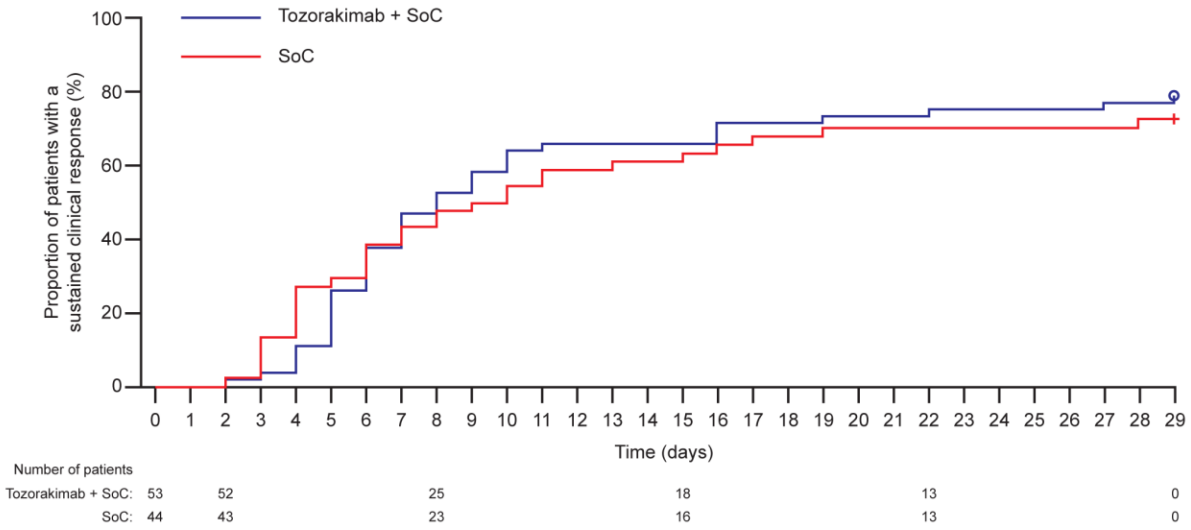

Tozorakimab + SoC
SoC
Proportion of patients with a sustained clinical response (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Time (days)
Number of patients
Tozorakimab + SoC: 53 52 25 18 13 0
SoC: 44 43 23 16 13 0

Figure 2

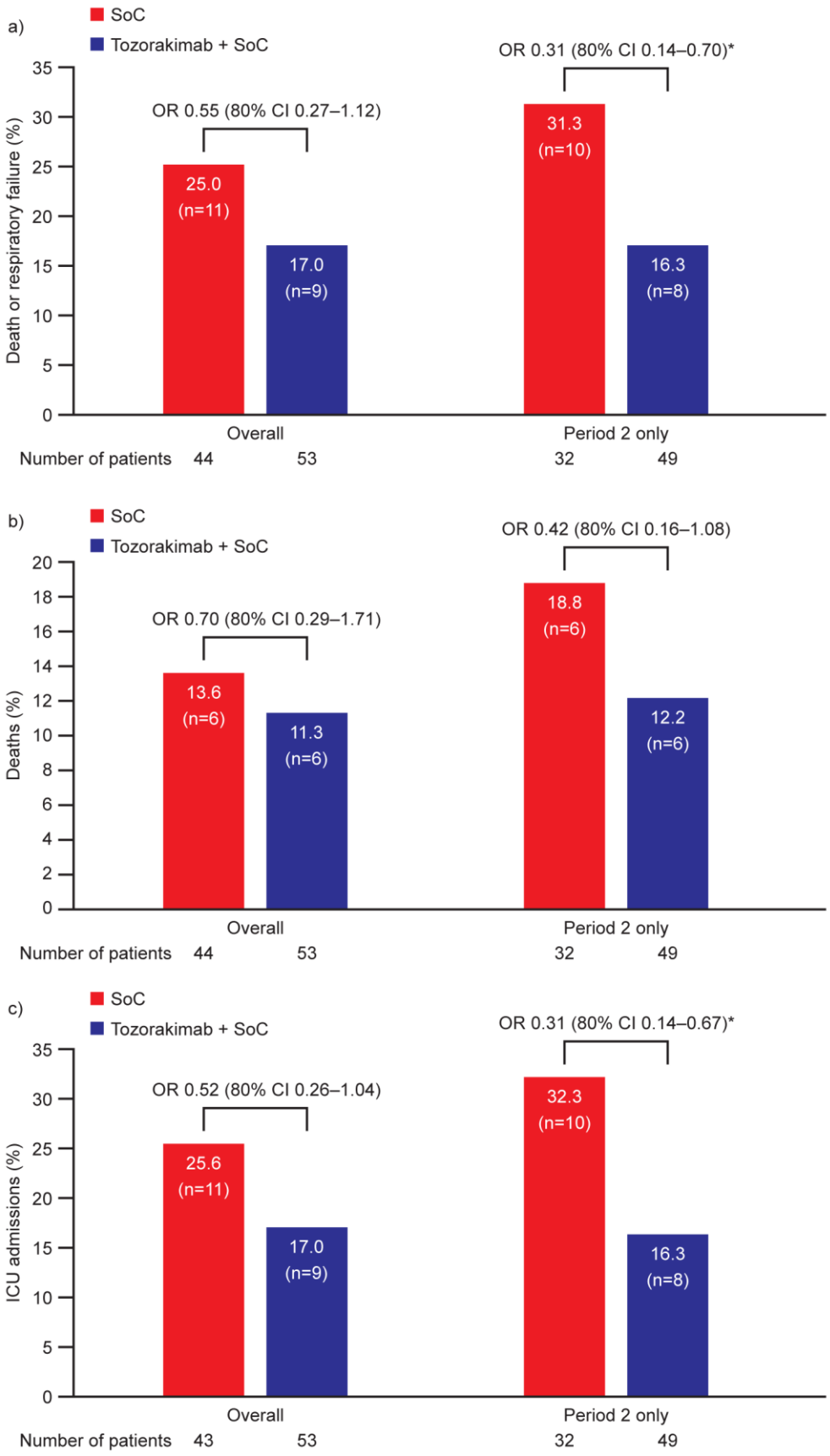

a)
SoC
Tozorakimab + SoC
OR 0.55 (80% CI 0.27–1.12)
OR 0.31 (80% CI 0.14–0.70)*
Death or respiratory failure (%)
25.0 (n=11)
17.0 (n=9)
31.3 (n=10)
16.3 (n=8)
Overall
Period 2 only
Number of patients 44 53 32 49
b)
SoC
Tozorakimab + SoC
OR 0.70 (80% CI 0.29–1.71)
OR 0.42 (80% CI 0.16–1.08)
Deaths (%)
13.6 (n=6)
11.3 (n=6)
18.8 (n=6)
12.2 (n=6)
Overall
Period 2 only
Number of patients 44 53 32 49
c)
SoC
Tozorakimab + SoC
OR 0.52 (80% CI 0.26–1.04)
OR 0.31 (80% CI 0.14–0.67)*
ICU admissions (%)
25.6 (n=11)
17.0 (n=9)
32.3 (n=10)
16.3 (n=8)
Overall
Period 2 only
Number of patients 43 53 32 49

Figure 3

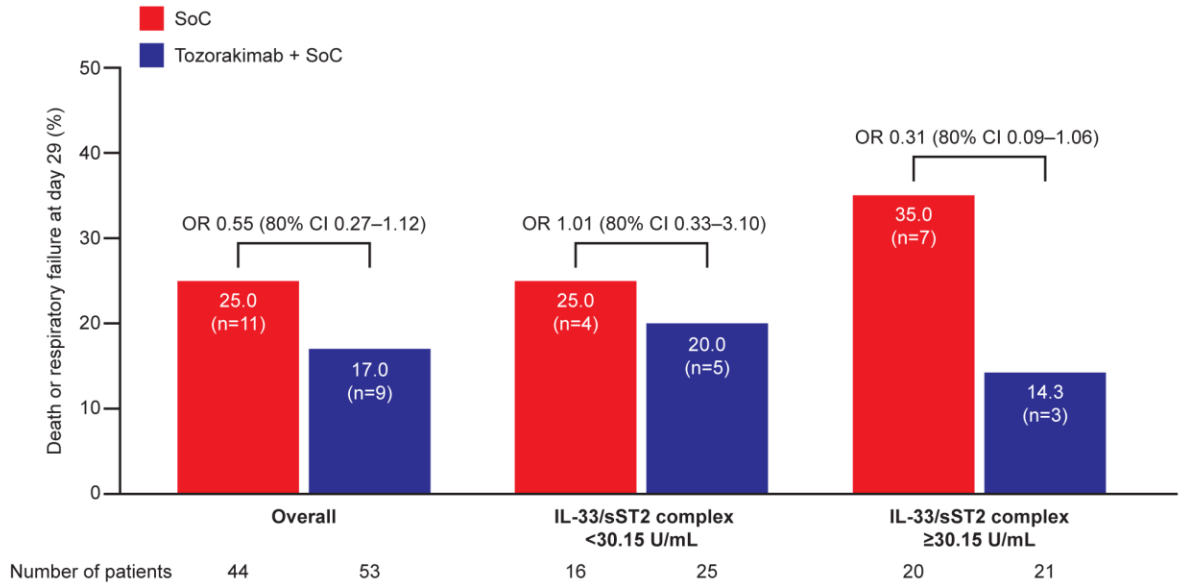

SoC
Tozorakimab + SoC
Death or respiratory failure at day 29 (%)
50
40
30
20
10
0
OR 0.55 (80% CI 0.27–1.12)
OR 1.01 (80% CI 0.33–3.10)
OR 0.31 (80% CI 0.09–1.06)
25.0 (n=11)
17.0 (n=9)
25.0 (n=4)
20.0 (n=5)
35.0 (n=7)
14.3 (n=3)
Overall
IL-33/sST2 complex <30.15 U/mL
IL-33/sST2 complex ≥30.15 U/mL
Number of patients
44
53
16
25
20
21

Figure 4

Supplementary appendix

Supplementary methods

Study design and participants

Patient enrolment for each agent arm continued until the planned enrolment target was achieved.

Inclusion and exclusion criteria

Inclusion criteria

1. Adults (aged ≥18 years) with severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection confirmed by laboratory tests and/or point of care tests.
2. A score of 3–5 on the 9-point World Health Organization ordinal scale.
3. The patient and their partner agreed to use medical-accepted double-barrier methods of contraception (*e.g.* barrier methods, including male condom, female condom or diaphragm with spermicidal gel) during the study and for at least 6 weeks after termination of study therapy. Having a vasectomised partner was considered an appropriate birth control method provided that the partner was the sole male sexual partner and the absence of sperm had been confirmed. If not, an additional method of contraception was used, or the patient was a woman who was not of childbearing potential.
4. Women who were lactating who agreed not to breastfeed their child during the study and for at least 6 weeks after termination of study therapy (they could continue to express milk away from the child during this period, but this milk must be discarded).
5. Ability to provide informed consent signed by the study patient or legally authorised representative.

Exclusion criteria

Patients were excluded from the study is any of the following criteria applied (or any of the criteria from the appropriate sub-protocol).

1. Patients who previously had a score of 6 or 7 on the 9-point ordinal scale.
2. Any patients whose interests were not best served by study participation as determined by a senior attending clinician.
3. Alanine aminotransferase/aspartate aminotransferase >5 x the upper limit of normal.
4. Known active infection with human immunodeficiency virus or hepatitis B or C.

5. Stage 4 severe chronic kidney disease or requiring dialysis (*i.e.* estimated glomerular filtration rate <30 mL/min/1.73 m^2).
6. History of the following cardiac conditions:
    a. myocardial infarction within 3 months prior to the first dose
    b. unstable angina
    c. history of clinically significant dysrhythmias (long QT features on electrocardiogram, sustained bradycardia [≤55 bpm]), left bundle branch block, cardiac pacemaker or ventricular arrhythmia) or history of familial long QT.
7. Screening 12-lead electrocardiogram with a measurable QTc interval according to Fridericia correction >500 ms.
8. Anticipated transfer to another hospital that was not a study centre within 72 hours.
9. Allergy to any study medication.
10. Experimental off-label usage of medicinal products as treatments for coronavirus disease 2019 (COVID-19).
11. Patients participating in another clinical study of an investigational medicinal product.
12. Active tuberculosis defined as requiring current treatment for tuberculosis.

Randomisation

Patients were randomly assigned to receive treatment with equal probability of randomisation to each of the study arms running at the study site at the time of enrolment. The study was open label, and both investigators and patients were aware of treatment allocation. The randomisation ratio was automatically adjusted, accounting for the number of study arms available at each study site, to ensure that the number of patients randomised to each candidate agent plus standard of care (SoC) was approximately equal to the number randomised to SoC alone. Patients were excluded from randomisation to a candidate agent if they did not meet the eligibility criteria specified in the sub-protocol. The allocation sequence was generated by Cenduit Interactive Response Technology with the electronic case report form assigned a unique randomisation number, linked to a treatment arm, to the patients. Randomisation was stratified by study centre and baseline disease severity grade.

Procedures

Based on phase 1 clinical pharmacokinetics data, a single 300 mg intravenous dose of tozorakimab was predicted to suppress IL-33 levels more than 99% at peak drug concentration in sputum. The optimal serum concentration for tozorakimab efficacy in patients with COVID-19 was not known at the start of enrolment. Rationale for administration of a second dose 14 days after the first dose was based on the approximate terminal half-life of tozorakimab and the results of a 4-week toxicology study, which predicted a highly favourable safety margin

(>47-fold) when a second dose of tozorakimab 300 mg was administered at this interval. SoC treatment in both study arms continued until hospital discharge. Administration of the second dose of tozorakimab when it would otherwise be required did not occur for the following reasons: patient request, protocol violation, any clinically significant adverse event (AE), any serious AE (SAE), severe laboratory test abnormality, pregnancy or deemed not to be in the best interest of the patient by the investigator.

SoC

Patients were enrolled by study site investigators and randomised to receive one of the candidate treatments being evaluated at that time or the SoC arm. SoC treatment during the study could include oral once-daily remdesivir for 5 days, once-daily dexamethasone until hospital discharge, or tocilizumab on top of dexamethasone, and respiratory support with supplemental oxygen or non-invasive ventilation. At each site, patients could receive either SoC or a candidate agent; therefore, the SoC arm was shared between the candidate experimental arms in the study.

Data for all treatment-emergent adverse events (TEAEs) and serious TEAEs were collected regardless of causality; events were managed according to physician judgement and applicable national guidelines. All serious TEAEs were followed until resolution, stabilisation or event explanation (if the patient was not lost to follow-up). Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, and were coded using the Medical Dictionary for Regulatory Activities, version 24.0. All SAEs were reported by the investigator to the sponsor within 24 hours of identification. COVID-19-related events that met the definition of SAEs did not require expedited reporting. Cardiovascular, renal and liver organ failure were reported as AEs of special interest in both study arms and serious hypersensitivity, hepatic function abnormality, cardiac events, serious infections, serious gastrointestinal events and malignancies were reported as Aes of special interest in the tozorakimab arm. In both study arms, clinical status, Aes, vital signs (body temperature, pulse, blood pressure, respiratory rate, oxygen saturation), concomitant medications and survival were monitored at baseline and daily until hospital discharge, and at day 15 and 29 if the patient was discharged before day 15. Blood gases (fraction of inspired oxygen and partial pressure of oxygen) followed the same schedule excluding day 29 if the patient had already been discharged.

The last day of these assessments while hospitalised was day 29. Physical examination was performed at screening and daily until hospital discharge (focusing on lung auscultation during treatment). Clinical status was assessed by the ordinal scale score, National Early Warning

Score 2 oxygen requirement and non-invasive or invasive ventilator requirement. Laboratory safety assessments (haematology, blood chemistry, liver function, coagulation) were performed at screening, at baseline and on days 3, 5, 8 and 11 while patients were hospitalised. Laboratory research assessments were performed at baseline and on day 5 and day 10 for inflammatory cytokine biomarker analysis and host transcriptome analyses, and at baseline and on day 15 for host serological SARS-CoV-2 response analysis. In the tozorakimab arm, further laboratory assessments were performed for pharmacokinetic and immunogenicity analyses.

The protocol only mandated laboratory safety assessments. SARS-CoV-2 infection was monitored by reverse transcription polymerase chain reaction from nasopharyngeal swab at baseline and on days 3, 5, 8, 11, 15 and 29. Study follow-up for Aes and survival occurred as outpatient visits at days 60 and 90. The aim was to perform all assessments unless the patient withdrew consent or was lost to follow-up.

Statistical analysis

Primary analysis was conducted in patients who were randomised, had at least one post-baseline ordinance scale score and received at least one dose of study medication (efficacy population). The primary method of statistical comparison was a stratified log-rank test.

Ties were handled using the exact method. Confidence intervals were calculated according to the Brookmeyer and Crowley method. There was no imputation of missing data.

Summary statistics and shift tables were generated for additional secondary endpoints. No adjustments for multiple testing were made.

All safety endpoints were evaluated in patients who underwent randomisation and received at least one dose of study medication, regardless of recording a post-baseline ordinal score (safety analysis set).

Independent data and safety monitoring committee

An independent data and safety monitoring committee was established to assess safety on an ongoing basis throughout the study. This committee held a formal review halfway through each recruitment period.

SUPPLEMENTARY TABLE 1 Baseline demographics and patient characteristics of patients enrolled in period 2 in the safety analysis set[a]

Demographic/characteristic	**Tozorakimab + SoC (n=50)**	**SoC (n=32)**
Age, years, mean (SD)	56.1 (12.4)	56.9 (13.7)
Age ≥70 years	8 (16.0)	6 (18.8)
Sex, male	34 (68.0)	21 (65.6)
Body mass index, kg/m^2, mean (SD)	31.6 (7.4)	32.7 (7.8)
Smoking status[b]		
Former	25 (50.0)	14 (45.2)
Current	2 (4.0)	0 (0.0)
Time since onset of symptoms		
<12 days	34 (68.0)	27 (84.4)
≥12 days	16 (32.0)	5 (15.6)
Derived baseline WHO OS score		
Grade 3	1 (2.0)	0 (0.0)
Grade 4	38 (76.0)	26 (81.3)
Grade 5	11 (22.0)	6 (18.8)
NEWS2 score, mean (SD)	4.7 (2.3)	4.1 (1.6)
Clinical frailty score at baseline		
Very fit	8 (16.0)	4 (12.5)
Well	21 (42.0)	13 (40.6)
Managing well	8 (16.0)	4 (12.5)
Vulnerable	4 (8.0)	1 (3.1)
Mildly frail	2 (4.0)	3 (9.4)
Moderately frail	7 (14.0)	7 (21.9)
Comorbidities at baseline		
≥1	32 (64.0)	18 (56.3)
≥2	20 (40.0)	9 (28.1)
Comorbidity categories		
Heart disease	5 (10.0)	3 (9.4)
Diabetes	20 (40.0)	10 (31.3)
Chronic lung disease	7 (14.0)	2 (6.3)
Chronic liver disease	1 (2.0)	0 (0.0)
Asthma[b]	7 (14.0)	5 (16.1)

Tuberculosis	0 (0.0)	1 (3.1)
Cancer	5 (10.0)	1 (3.1)
Hypertension	15 (30.0)	9 (28.1)
Remdesivir at baseline	32 (64.0)	22 (68.8)
Dexamethasone at baseline	50 (100.0)	31 (96.9)
Supplemental oxygen at baseline	49 (98.0)	32 (100.0)
Received COVID-19 vaccine during the study	13 (26.0)	4 (12.5)

Data are presented as n (%) unless stated otherwise. [a]Percent values are based on the safety analysis set. One patient in the tozorakimab arm did not have a post-dose OS assessment and was excluded from the full analysis set but included in the safety analysis set. [b]Percent values are based on 50 patients receiving tozorakimab and 31 patients receiving SoC. COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; NEWS: National Early Warning Score; OS: ordinal scale; SD: standard deviation; SoC: standard of care; WHO: World Health Organization.

SUPPLEMENTARY TABLE 2 Mortality at days 15, 29 and 60

	Tozorakimab + SoC (N=53)	**SoC (N=44)**	**P value**
Day 15			
Mortality, n (%)	3 (5.7)	4 (9.1)	
Odds ratio (80% CI)	0.45 (0.14–1.39)	NA	0.42
Day 29			
Mortality, n (%)	6 (11.3)	6 (13.6)	
Odds ratio (80% CI)	0.70 (0.29–1.71)	NA	0.62
Day 60			
Mortality, n (%)	8 (15.1)	9 (20.5)	
Odds ratio (80% CI)	0.60 (0.27–1.33)	NA	0.38

CI: confidence interval; NA: not available; SoC: standard of care.

SUPPLEMENTARY TABLE 3 Non-deterioration in OS score on days 15 and 29

	Tozorakimab + SoC (N=53)	**SoC (N=44)**	**P value**
Day 15			
No deterioration by at least 1 point on the OS, n (%)	45 (84.9)	34 (77.3)	
Odds ratio (80% CI)	1.83 (0.89–3.76)	NA	0.27
Day 15			
No deterioration by at least 2 points on the OS, n (%)	46 (86.8)	35 (79.5)	
Odds ratio (80% CI)	1.77 (0.85–3.67)	NA	0.30
Day 15			
No deterioration by at least 3 points on the OS, n (%)	48 (90.6)	40 (90.9)	
Odds ratio (80% CI)	1.04 (0.40–2.70)	NA	0.97
Day 29			
No deterioration by at least 1 point on the OS, n (%)	44 (83.0)	33 (75.0)	
Odds ratio (80% CI)	1.81 (0.89–3.68)	NA	0.26
Day 29			
No deterioration by at least 2 points on the OS, n (%)	45 (84.9)	33 (75.0)	
Odds ratio (80% CI)	2.07 (1.02–4.21)	NA	0.18
Day 29			
No deterioration by at least 3 points on the OS, n (%)	47 (88.7)	36 (81.8)	
Odds ratio (80% CI)	2.02 (0.88–4.64)	NA	0.27

CI: confidence interval; NA: not available; OS: World Health Organization ordinal scale; SoC: standard of care.

SUPPLEMENTARY TABLE 4 Time to sustained live discharge from hospital

	Tozorakimab + SoC (N=53)	**SoC (N=44)**	**P value**
Patients with sustained live discharge from hospital, n (%)	44 (83.0)	35 (79.5)	
Patients with censored data, n (%)	9 (17.0)	9 (20.5)	
Median, days	8.0	9.5	
HR (80% CI)	0.92 (0.68–1.25)	NA	0.79

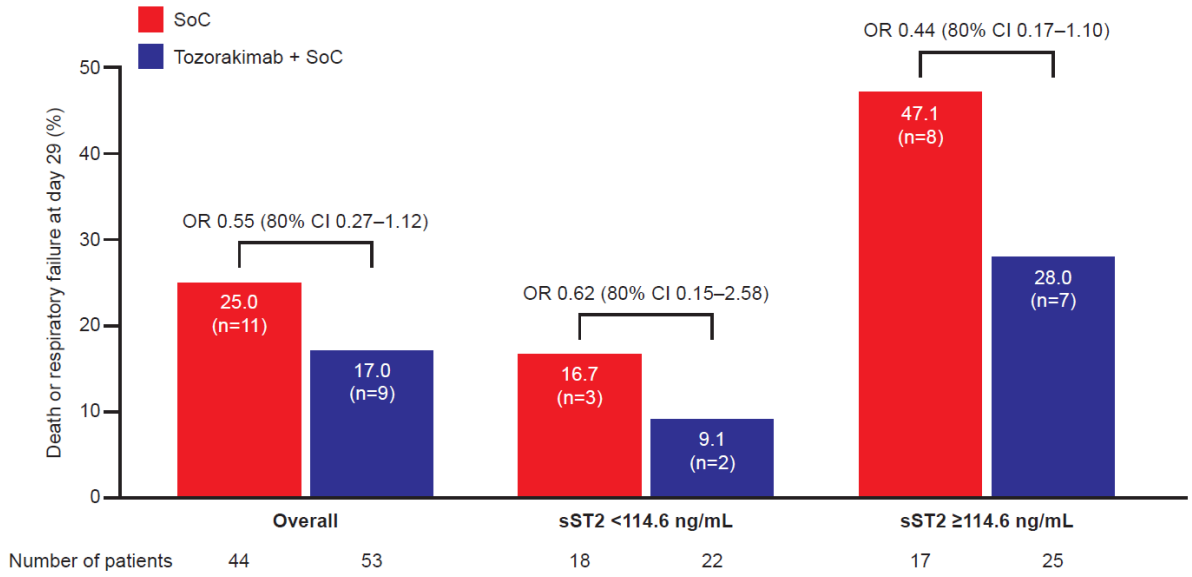
CI: confidence interval; HR: hazard ratio; NA: not available; SoC: standard of care.

SUPPLEMENTARY TABLE 5 Duration of ventilation use

	Tozorakimab + SoC (N=53)	**SoC (N=44)**
Duration of ventilation use, days	1.8 (5.3)	3.1 (7.2)
Percentage of days on ventilation	7.7 (21.3)	12.4 (26.0)
Number of ventilation-free days	25.6 (8.0)	24.0 (9.3)
Percentage of ventilation-free days	92.3 (21.3)	87.6 (26.0)

Data are mean (standard deviation). SoC: standard of care.

SUPPLEMENTARY FIGURE 1 Death or respiratory failure at day 29 by baseline level of sST2.



Some patients had missing biomarker values at baseline. The cut-off is the median baseline sST2 value. RR was calculated directly from observed proportions, without adjustment for other factors. OR was calculated from a logistic regression model adjusting for age and baseline severity. CI: confidence interval; OR: odds ratio; SoC: standard of care; sST2: soluble ST2.