9-2-2024

The IL-6 hypothesis in COVID-19: A phase 2, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of free IL-6 sequestration by the monoclonal antibody sirukumab in severe and critical COVID-19

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Journal of Infection 89 (2024) 106241

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Infectious Disease Practice

The IL-6 hypothesis in COVID-19: A phase 2, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of free IL-6 sequestration by the monoclonal antibody sirukumab in severe and critical COVID-19

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ARTICLE INFO

Article history:
Accepted 1 August 2024
Available online 2 September 2024

SUMMARY

Background: Upregulation of IL-6 has been associated with worse prognosis in COVID-19 patients. Impact on IL-6 signalling has mostly been limited to clinical outcomes in IL-6 receptor antagonist trials.
Methods: We performed a phase 2, randomised, double-blind, placebo-controlled trial (NCT04380961) of US-based hospitalised adults (< 85 years) with laboratory-confirmed SARS-CoV-2 infection and severe (low

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https://doi.org/10.1016/j.jinf.2024.106241

Keywords:
COVID-19
IL-6
Sirukumab

levels of supplemental oxygen) or critical disease (high levels of oxygen supplementation). Patients received sirukumab 5 mg/kg or placebo single dose IV on Day 1 plus standard of care. The primary endpoint was time to sustained clinical improvement up to Day 28 based on an ordinal scale. Secondary endpoints included clinical improvement, all-cause mortality, and safety. Following an interim analysis, the protocol was amended to only recruit patients with critical COVID-19.

Findings: From May 2020 to March 2021, 209 patients were randomised; 112 had critical disease (72 sirukumab, 40 placebo) at baseline. Median time to sustained clinical improvement in critical patients was 17 and 23 days in the sirukumab and placebo groups (HR, 1·1; 95% CI, 0·66–1·88; p > 0·05). At Day 28, 59·4% versus 55·0% of patients achieved clinical improvement with sirukumab versus placebo and rates of all-cause mortality were 24·6% versus 30·0%, respectively. Rates of grade ≥3 adverse events were comparable between the sirukumab and placebo groups (25·9% vs 32·9%; all patients).

Interpretation: In critical COVID-19 patients who received sirukumab, there was no statistically significant difference in time to sustained clinical improvement versus placebo despite objective sequestration of circulating IL-6, questioning IL-6 as a key therapeutic target in COVID-19.

Introduction

Respiratory failure is a leading cause of mortality from coronavirus disease 2019 (COVID-19).[1] As early as May 2020, the antiviral, remdesivir, demonstrated a reduced time to clinical recovery in the pivotal ACTT-1 randomised controlled trial and is currently recommended for patients with non critical COVID-19 (i.e., those who do not require invasive ventilation).[2,3] Systemic inflammation is associated with worse clinical outcomes in patients hospitalised for COVID-19.[4–6] Thus, corticosteroids such as dexamethasone were tested early in the pandemic and found to be effective in reducing mortality in patients receiving supplemental oxygen or invasive mechanical ventilation.[7] Despite the effectiveness of such therapies in decreasing mortality,[8] there remained an unmet need for further immunomodulation of the dysregulated host response in COVID-19 pneumonia with hypoxaemia. Guidelines for the management of COVID-19 with hypoxaemia rapidly incorporated therapies that reduce inflammation, including corticosteroids and immunomodulatory agents[2,9] and have been continuously updated based on available clinical evidence to incorporate other immunomodulatory agents and selective, tiered anticoagulation strategies, such as the use of heparin.

Clinical observations suggest that upregulation of interleukin-6 (IL-6) is associated with COVID-19 disease severity, and early data led to the hypothesis that blockade of the IL-6 pathway would benefit COVID-19 patients.[10–13] Multiple clinical studies have assessed the efficacy of IL-6 receptor antagonists, such as the anti-IL-6–receptor monoclonal antibodies (mAbs) tocilizumab and sarilumab in COVID-19 patients.[13–15] At the individual trial level, results have been mixed, although several meta-analyses of patients hospitalised for COVID-19 suggest that administration of IL-6 pathway antagonists was associated with a small, but significant, reduction in mortality.[16–18] One meta-analysis of 10,930 patients reported a significantly lower 28-day all-cause mortality (odds ratio, 0·86; 95% confidence interval [CI], 0·79–0·95),[16] which is reflected in guidelines; sarilumab and tocilizumab are recommended by the World Health Organization (WHO) and the National Institutes of Health (NIH) for the treatment of COVID-19.[2,9] Tocilizumab has been approved in the United States and by the European Medicines Agency (EMA) for the treatment of hospitalised adults with COVID-19.[19,20] Clinical trial evidence shows the benefit of other immunomodulators (e.g., the JAK/STAT inhibitor baricitinib) in critical COVID-19, therefore supporting the contribution of cytokine dysregulation to disease pathogenesis.[18,21] However, previous randomised controlled studies have not specifically examined the IL-6 hypothesis that asks whether elevated IL-6 is a direct, therapeutically modifiable target to mitigate clinical risk in patients with critical COVID-19. Sirukumab offers the unique ability to assess circulating IL-6 levels upstream of the IL-6 receptor.

Sirukumab is a mAb that binds IL-6 with high affinity and neutralises IL-6 by preventing its association with the IL-6 receptor,[22] acting one step upstream from the anti-IL-6–receptor mAbs. This allows the direct assessment of free (unbound) IL-6 levels upon IL-6 signalling modulation, a key unmet need in understanding the role of IL-6 in COVID-19 pathogenesis. This trial, which enrolled patients between May 2020 and March 2021, evaluated the efficacy and safety of sirukumab in hospitalised adult patients with severe (requiring oxygen supplementation) or critical (requiring high levels of oxygen supplementation) COVID-19.

Methods

Study design

This was a phase 2, randomised, double-blind, placebo-controlled trial (ClinicalTrials.gov identifier: NCT04380961). The study was conducted at 13 centres in the United States. Ethics approval was obtained at each study site.

Patients

Patients were US-based hospitalised adults aged ≥18 to < 85 years with laboratory-confirmed SARS-CoV-2 infection (as determined by real-time polymerase chain reaction [PCR] at any time before randomisation) and severe or critical disease. Patients were enrolled between May 2020 and March 2021; patients who received investigational or emergency-use authorised vaccines against SARS-CoV-2 were excluded. Severe disease was defined as requiring a low level of supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device (i.e., above the pre–COVID-19 baseline oxygen requirement, if any, by the patient). Critical disease was defined as requiring high levels of oxygen supplementation to sustain a blood oxygen saturation of > 93% provided by either nonrebreather mask or high-flow nasal cannula (with fraction of inspired oxygen of 50% or higher), use of non-invasive ventilation or invasive mechanical ventilation (IMV), and/or veno-venous extracorporeal membrane oxygenation (ECMO).

Randomisation and masking

Central randomisation was implemented using a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor. The participants, study-site personnel, and investigators were blinded to treatment allocation throughout the study, except for the designated pharmacist(s) or independent qualified staff member(s) with primary responsibility for study drug preparation.

Patients were randomised 2:1 to receive sirukumab 5 mg/kg intravenous (IV) single-dose infusion on Day 1 plus standard-of-care (SOC) treatment or placebo single dose on Day 1 plus SOC. SOC was determined by investigators based on evolving local practice and

consisted of supportive care and included antithrombotic agents, remdesivir or other direct antivirals as available, and high-frequency use of glucocorticoids. Participation in a single arm study or compassionate use study was allowed only if it was conducted with one of the antiviral drugs with demonstrated in vitro effect against SARS-CoV-2. Patients were excluded if they were on IMV for > 24 h at the time of screening, met local or global criteria to not receive mechanical ventilation, had designated themselves as do not resuscitate per a living will, or received an investigational intervention or used an invasive investigational medical device within 30 days before the planned first dose of study intervention. Randomisation was stratified by age (< 65 and ≥65 years) and by IMV (yes/no) at the time of randomisation.

A Data Monitoring Committee (DMC) was established to actively monitor interim data, to review ongoing safety, and to make recommendations about early study closure or change to the conduct of the study. The committee consisted of sponsor personnel not directly involved in the conduct of the study with expertise in clinical study conduct and included at least one expert in infectious diseases, one statistician, a safety expert, and three external experts. Following efficacy signals observed at an interim analysis by the DMC when 61 patients had reached Day 28, the clinical protocol was amended to continue recruitment of patients with critical COVID-19 only, until approximately 111 patients with critical COVID-19 were enrolled. The study was conducted per the Declarations of Helsinki and Good Clinical Practice guidelines. All patients or legally acceptable representatives provided written informed consent.

Endpoints

The primary endpoint was time to sustained clinical improvement up to Day 28; improvement was to be sustained until Day 28, discharge, or discontinuation (whichever was first). As the trial was initiated early in the pandemic prior to relatively uniform coalescence around the WHO ordinal score, clinical improvement was defined as an improvement of at least two categories relative to baseline on a trial-specific 6-point ordinal clinical recovery scale (OS): 1–not hospitalised; 2–hospitalised, not requiring supplemental oxygen (mild disease); 3–hospitalised, requiring low-flow supplemental oxygen (severe disease); 4–hospitalised, on noninvasive pressure ventilation, non rebreather mask, or high-flow oxygen devices (critical disease); 5–hospitalised, on IMV or ECMO (critical disease); 6–death. Key secondary endpoints included clinical improvement at Day 28 and all-cause mortality at Day 28. Other secondary endpoints included additional clinical efficacy and safety parameters; exploratory endpoints included parameters in virology, biomarkers (e.g., free IL-6 and C-reactive protein [CRP]), pharmacokinetics (PK), and immunogenicity.

Assessments

Efficacy was assessed daily via the 6-point OS up to Day 28, hospital discharge, or study discontinuation (whichever came first). Patients discharged before Day 28 received a follow-up phone call on Day 28. Additional follow-up was conducted by phone at Weeks 8, 12, and 16. Safety evaluations were conducted throughout the study, from obtaining confirmed consent until the last study-related activity. Safety evaluations included monitoring of adverse events (AEs), serious AEs, and clinical laboratory parameters. AEs of special interest included serious infection, hypersensitivity, haematologic events, and liver enzymes.

Serum samples were used to evaluate sirukumab PK, free IL-6 and CRP levels, and immunogenicity (presence of anti-sirukumab antibodies). PK and immunogenicity were evaluated in all patients who received sirukumab. Values less than the lower limit of quantitation (LLOQ) were imputed as LLOQ/2; values greater than the upper limit of quantitation (ULOQ) were imputed as ULOQ.

SARS-CoV-2 viral RNA copy number was measured by quantitative reverse-transcriptase PCR (qRT-PCR) in samples obtained from nasopharyngeal swabs. The LLOQ value for the viral copy number assay on nasopharyngeal swabs was 1018 copies/mL. Measurements below the LLOQ were imputed as 1 copy/mL if the viral RNA was undetectable or as LLOQ/2 if the viral RNA was detectable but not quantifiable. SARS-CoV-2 viral genome sequence analysis was performed using next generation sequencing following the ARTIC primers/protocol on the Illumina (San Diego, CA) platform to evaluate the presence of genetic variations. Genetic variations were defined as codon changes from the SARS-CoV-2 Wuhan-Hu1 reference sequence.[23] Sequence results are presented only for the spike protein. The SARS-CoV-2 variants analysed were B.1.526, B.1.525, P.2, B.1.1.7, P.1, B.1.351, B.1.427, B.1.429, B.1.617, B.1.617.1, B.1.617.2, and B.1.617.3.

Statistical analysis

Per the amended protocol, the study aimed to enrol approximately 111 patients with confirmed critical COVID-19 at a 2:1 randomisation ratio to sirukumab plus SOC or placebo plus SOC. It was assumed that for the survivors in the control arm, the log-transformed time to sustained clinical improvement (days) followed a normal distribution with mean of log 28 and standard deviation of 0.9. Power calculations assumed sirukumab would reduce the median time to sustained clinical improvement from 28 to 16·8 days (40% reduction) in the surviving patients and was assumed to have the same standard deviation of 0·9. The control arm mortality rate was assumed to be 40% up to Day 28; sirukumab was assumed to reduce the mortality with an absolute difference of 20% (from 40% to 20%; 50% relative reduction). Based on these assumptions, at least 111 patients with confirmed critical COVID-19 were required to have at least 80% power to demonstrate a difference in time to sustained clinical improvement between both treatment arms per log-rank test at a two-sided significance level of 5%.

Descriptive statistics by treatment group were provided for the different analysis sets. The All Patients Analysis Set included all patients who were randomised and treated in the study; it was used for the efficacy and safety analysis. The Critical Patients Analysis Set consisted of all participants in the All Patients Analysis Set with confirmed critical COVID-19, defined as a score of 4 or 5 on the OS at baseline.

A hierarchical testing strategy was planned for the primary and key secondary endpoints. Statistical tests were stratified by age (< 65 and ≥65 years) and use of IMV (yes/no). The primary endpoint was tested for superiority using a stratified log-rank test at the two-sided 5% significance level. The hazard ratio (HR) of sustained clinical improvement for sirukumab plus SOC versus placebo plus SOC from baseline until Day 28 was considered the population-level summary measure of the treatment effect. Participants who discontinued before Day 28 were included with their last observed score. Participants who discontinued the trial before Day 28 with an OS score > 1 were considered as death.

The effects of covariates were examined on the time to sustained clinical improvement in a Cox proportional hazards model, and on clinical improvement and all-cause mortality at Day 28 in logistic regression models. The models were adjusted for the stratification factors (age and mechanical ventilation), treatment, and an additional single covariate (sex, race, ethnicity, baseline OS, remdesivir use at baseline, glucocorticoid use at baseline, and number of comorbidities). Safety and exploratory endpoints were analysed using descriptive statistics.

Table 1
Baseline demographic and disease characteristics.[a]

	Critical Patients		All Patients	
	Sirukumab + SOC (n = 72)	Placebo + SOC (n = 40)	Sirukumab + SOC (N = 139)	Placebo + SOC (N = 70)
Age	n = 72	n = 40	n = 139	n = 70
Median (range), years	60·0 (27–84)	58·0 (31–82)	58·0 (18–84)	58·0 (31–82)
≥65 years, n (%)	28 (38·9)	12 (30·0)	45 (32·4)	22 (31·4)
Sex, n (%)	n = 72	n = 40	n = 139	n = 70
Male	56 (77·8)	25 (62·5)	98 (70·5)	45 (64·3)
Race, n (%)	n = 70	n = 37	n = 130	n = 65
American Indian or Alaska Native	1 (1·4)	0	1 (0·8)	0
Asian	3 (4·3)	2 (5·4)	7 (5·4)	3 (4·6)
Black or African American	9 (12·9)	8 (21·6)	18 (13·8)	11 (16·9)
White	57 (81·4)	27 (73·0)	104 (80·0)	51 (78·5)
Ethnicity, n (%)	n = 72	n = 40	n = 139	n = 70
Hispanic or Latino	32 (44·4)	21 (52·5)	64 (46·0)	36 (51·4)
Body mass index, kg/m^2	n = 71	n = 39	n = 138	n = 69
Median (range)	32·3 (19·0–69·2)	33·1 (22·8–54·8)	31·8 (19·0–69·2)	31·7 (20·5–54·8)
Days from onset of first symptoms to randomisation	n = 72	n = 40	n = 139	n = 70
Mean (SD)	9·85 (4·77)	9·18 (5·14)	9·81 (4·88)	8·96 (4·37)
Median (range)	9·0 (1–21)	8·5 (1–25)	9·0 (1–26)	9·0 (1–25)
Chest imaging (x-ray, CT scan, echo, or NMR scan),[b] n (%)	n = 69	n = 39	n = 135	n = 69
Normal	1 (1·4)	0	2 (1·5)	0
Abnormal[c]	68 (98·6)	39 (100)	133 (98·5)	69 (100)
Unilateral findings	1 (1·5)	1 (2·6)	5 (3·8)	3 (4·3)
Bilateral findings[d]	65 (95·6)	38 (97·4)	125 (94·0)	66 (95·7)
Ordinal scale at randomisation, n (%)	n = 72	n = 40	n = 139	n = 70
2: Hospitalised, not requiring supplemental oxygen	0 (0)	0 (0)	1 (0·7)	2 (2·9)
3: Hospitalised, requiring low flow supplemental oxygen	0 (0)	0 (0)	66 (47·5)	28 (40·0)
4: Hospitalised, on noninvasive pressure ventilation or high-flow oxygen devices	60 (83·3)	32 (80·0)	60 (43·2)	32 (45·7)
5: Hospitalised, on IMV or ECMO	12 (16·7)	8 (20·0)	12 (8·6)	8 (11·4)
IMV, n (%)	10 (13·9)	6 (15·0)	10 (7·2)	6 (8·6)
Concomitant medications of interest for COVID-19, n (%)				
COVID-19 direct antiviral	53 (73·6)	31 (77·5)	113 (81·3)	60 (85·7)
Remdesivir and glucocorticoids	53 (73·6)	30 (75·0)	109 (78·4)	57 (81·4)
Glucocorticoids for systemic use	69 (95·8)	39 (97·5)	131 (94·2)	67 (95·7)
Antibacterials for systemic use	45 (62·5)	26 (65·0)	63 (45·3)	37 (52·9)
Antimycotics for systemic use	9 (12·5)	6 (15·0)	9 (6·5)	6 (8·6)
Antithrombotic agents (excluding antiplatelets)	72 (100)	39 (97·5)	137 (98·6)	67 (95·7)
COVID-19 vaccine	2 (2·8)	0	4 (2·9)	2 (2·9)
Convalescent plasma	4 (5·6)	3 (7·5)	6 (4·3)	4 (5·7)
IL-6 receptor inhibitor	0	0	0	1 (1·4)[e]
Baseline CRP (mg/L), geometric mean (GSE)	109·9 (1·14)	112·3 (1·13)	88·9 (1·11)	96·4 (1·12)
Baseline IL-6 (ng/L), geometric mean (GSE)	5·33 (1·13)	4·73 (1·21)	4·04 (1·09)	3·81 (1·15)

COVID, coronavirus disease; CRP, C-reactive protein; CT, computed tomography; echo, echocardiogram; ECMO, extracorporeal membrane oxygenation; GSE, geometric standard error; IL-6, interleukin-6; IMV, invasive mechanical ventilation; NMR, nuclear magnetic resonance; SD, standard deviation; SOC, standard of care.
[a] Results are based on nonmissing data.
[b] Chest imaging: findings include verbatim, such as infiltrates, opacities, COVID, and pneumonia.
[c] Abnormal also includes patients with no unilateral or bilateral specifications available.
[d] When both unilateral and bilateral findings were detected, the patient was considered to have bilateral findings.
[e] Concomitant anti-IL-6 receptor was considered a protocol deviation.

Role of funding source

The funder of the study (Janssen Global Services, LLC) was involved in the study design, data collection, data analysis, and data interpretation, and provided support to a medical writer for writing and editing support.

Results

Patients

A total of 222 patients were screened for the study; 209 (94·1%) were enrolled between May 2020 and March 2021. Of these, 139 patients were randomised to sirukumab plus SOC, and 70 were randomised to placebo plus SOC and received one dose. Of the 209 randomised and treated patients, 112 (53·6%) had critical disease (Critical Patients: 72 sirukumab plus SOC; 40 placebo plus SOC). Fifty-three (47·3%) and 70 (33·5%) patients in the Critical Patients population and All Patients populations, respectively, prematurely discontinued the study. Main reasons were death (32·1%) and loss to follow-up (11·6%; Supplemental Table 1). No incorrect treatment was reported; all patients were treated as randomised. Baseline demographic and disease characteristics were balanced between the sirukumab and placebo groups for the Critical Patients and the All Patients populations (Table 1).

Critical Patients

Overall, the majority of Critical Patients were male (72·3%), White (78·5%), and obese (68·2%; Table 1). The population was ethnically diverse; 47·3% of patients identified as Hispanic or Latino. The median age was 59 years. At baseline, most patients were category 4 on the OS in the sirukumab group (83·3% [60/72]) and the placebo group (80·0% [32/40]). Almost all patients received concomitant medication for COVID-19; the most common medications were antithrombotic agents (99·1%), glucocorticoids (96·4%), and direct antiviral agents (75·0%). A minority of patients were on IMV at baseline

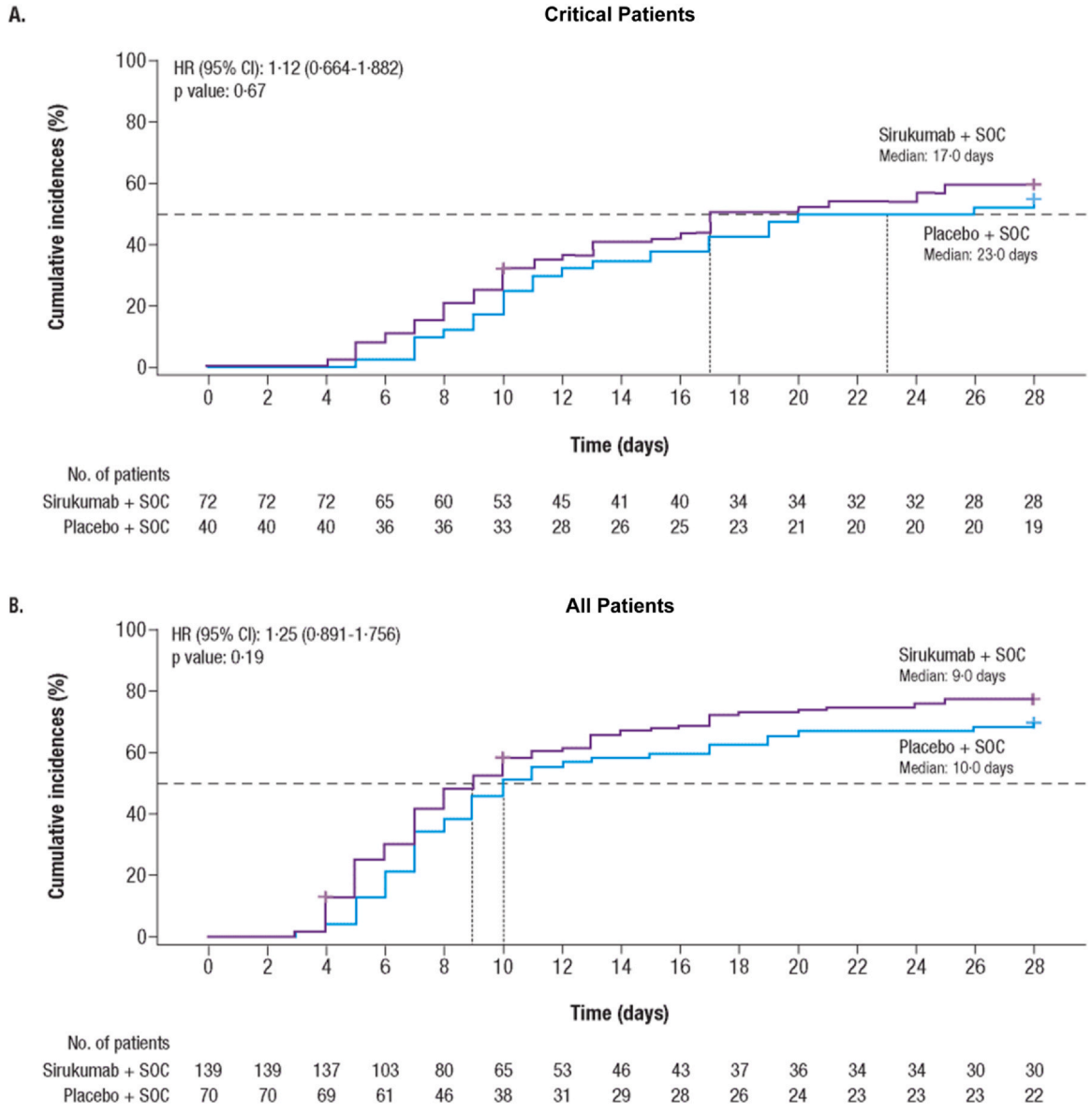

Fig. 1. Time to sustained clinical improvement up to Day 28 in (A) Critical and (B) All Patients treated with sirukumab or placebo. CI, confidence interval; HR, hazard ratio; SOC, standard of care.

(14·3%). The geometric mean CRP level at baseline was 109·9 mg/L (geometric standard error [GSE] = 1·14 mg/L) in the sirukumab group and 112·3 mg/L (GSE = 1·13 mg/L) in the placebo group. The geometric mean IL-6 level at baseline was 5·33 ng/L (GSE = 1·13 ng/L) and 4·73 ng/L (GSE = 1·21 ng/L) in the sirukumab and placebo groups, respectively.

All Patients

The baseline demographic and disease characteristics for the All Patients population were similar to those in the Critical Patients population, except that OS category 2 or 3 patients were seen in the All Patients population, in addition to the category 4 or 5 patients in the Critical Patients population (Table 1). Most patients were classified as OS category 3 or 4: 47·5% and 40·0% of patients in the sirukumab and placebo groups, respectively, had OS category 3 disease; 43·2% and 45·7% of patients in the sirukumab and placebo groups had OS category 4 disease. A minority had OS category 5 disease (8·6% and 11·4% in the sirukumab and placebo groups, respectively). CRP and IL-6 levels at baseline were slightly lower for All Patients compared with Critical Patients. The geometric mean CRP level was 88·9 mg/L (GSE = 1·11 mg/L) in the sirukumab group and 96·4 mg/L (GSE = 1·12 mg/L) in the placebo group. The geometric mean IL-6 level was 4·04 ng/L (GSE = 1·09 ng/L) and 3·81 ng/L (GSE = 1·15 ng/L) in the sirukumab and placebo groups, respectively.

Efficacy

Results of the primary efficacy analysis are shown in Fig. 1. In Critical Patients, the median time to sustained clinical improvement was 17 days in the sirukumab group and 23 days in the placebo group (HR, 1·1; 95% CI, 0·66–1·88); this difference was not statistically significant based on the log-rank test. Similarly, for All Patients, the median time to sustained clinical improvement was 9 days in the sirukumab group and 10 days in the placebo group (HR, 1·3; 95% CI, 0·89–1·76); the difference was also not statistically significant.

Key secondary efficacy analysis results are presented in Table 2. For Critical Patients, clinical improvement at Day 28 was seen in 59·4% (41/69) and 55·0% (22/40) of patients in the sirukumab and placebo groups, respectively. On this day, data were missing for three patients in the sirukumab group and no patients in the placebo

Table 2
Key secondary endpoints.

	Critical Patients		All Patients	
	Sirukumab + SOC (n = 72)	Placebo + SOC (n = 40)	Sirukumab + SOC (N = 139)	Placebo + SOC (N = 70)
Clinical improvement at Day 28				
Observed values, n (%)	n = 69	n = 40	n = 136	n = 70
Yes	41 (59·4)	22 (55·0)	106 (77·9)	49 (70·0)
No	28 (40·6)	18 (45·0)	30 (22·1)	21 (30·0)
Differences in proportions,[a] %				
Δ (90% CI)	1·88 (−14·15 to 17·90)		6·6 (−4·06 to 17·37)	
p value	0·849		0·298	
Risk ratio[a] (90% CI)	1·03 (0·78–1·36)		1·09 (0·94–1·27)	
All-cause mortality up to Day 28				
Observed values, n (%)	n = 69	n = 40	n = 136	n = 70
Yes	17 (24·6)	12 (30·0)	18 (13·2)	13 (18·6)
No	52 (75·4)	28 (70·0)	118 (86·8)	57 (81·4)
Differences in proportions,[b] %				
Δ (90% CI)	−2·16 (−16·48 to 12·16)		−2·98 (−11·72 to 5·76)	
p value	0·806		0·570	
Risk ratio[b] (90% CI)	0·93 (0·56–1·54)		0·84 (0·50–1·39)	

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IMV, invasive mechanical ventilation; SOC, standard of care.

[a] From a CMH analysis for differences in proportions adjusted for age (< 65 and ≥65 years) and use of IMV (yes/no). Patients who discontinued before Day 28 were included in the CMH analysis with their last observed score.

[b] From a CMH analysis for differences in proportions adjusted for age (< 65 and ≥65 years) and use of IMV (yes/no). Patients who discontinued the study before Day 28 with a score > 1 on the clinical recovery scale were considered dead.

group. For All Patients at Day 28, clinical improvement was seen in 77·9% (106/136) and 70·0% (49/70) of patients in the sirukumab and placebo groups, respectively. For Critical Patients, all-cause mortality at Day 28 was 24·6% (17/69) and 30·0% (12/40) in the sirukumab and placebo groups, respectively (Supplemental Figure 1). For All Patients, all-cause mortality at Day 28 was 13·2% (18/136) and 18·6% (13/70) in the sirukumab and placebo groups, respectively.

Results from the covariate analysis are shown in Supplemental Table 2. Of all the covariates examined, only baseline OS (2–3 vs 4 vs 5) seemed to have an effect on time to sustained clinical improvement, clinical improvement at Day 28, and all-cause mortality at Day 28 (primary and secondary endpoints). Sex, race, ethnicity, remdesivir use at baseline, glucocorticoids use at baseline, and the number of comorbidities did not appear to have an effect on the primary or key secondary endpoints.

Biomarkers

Baseline IL-6 levels are shown in Table 1. Treatment led to a decrease to undetectable free IL-6 levels from baseline in most patients compared with placebo on study Days 14, 21, and 28 for both the Critical Patient (Fig. 2A) and All Patient (Fig. 2B) populations. Patients who received placebo showed reduction of CRP levels over time (Days 3, 5, 7, 14, and 21 compared with baseline). CRP levels were further reduced in Critical Patients (Fig. 3A) and All Patients (Fig. 3B) who received sirukumab compared with placebo.

Virology

Viral RNA copy number over time for the Critical Patients and All Patients groups is shown in Supplemental Figure 2. For the Critical Patients, on Day 28 the mean change from baseline of the viral load was −4·67 $\log_{10}$ copies/mL in the sirukumab group and −4·09 $\log_{10}$ copies/mL in the placebo group. For all patients, on Day 28, the mean change from baseline of the viral RNA copy number was −4·47 $\log_{10}$ copies/mL in the sirukumab group and −4·09 $\log_{10}$ copies/mL in the placebo group.

For 79 and 43 patients in the sirukumab and placebo groups, respectively, a viral sequence of the spike region of the SARS-CoV-2 virus could be obtained. Genetic variations were defined as amino acid changes from the SARS-CoV-2 Wuhan-Hu1 reference sequence.[23] Two of 79 patients in the sirukumab group (2·5%) were found to have the B.1.429 (Epsilon) variant. In the placebo group, two of the 43 (4·7%) patients were found to have the B.1.1.7 (Alpha) variant and one (2·3%) patient had the B.1.429 variant.

Pharmacokinetics

PK analysis showed a steady decrease in the serum concentration of sirukumab over time (Supplemental Figure 3A). There was no apparent impact of baseline IL-6 level on sirukumab concentrations (Supplemental Figure 3B). With respect to immunogenicity, no antidrug antibodies were detected; of the patients who received sirukumab and had appropriate samples tested, none (0/96) demonstrated antibodies to sirukumab.

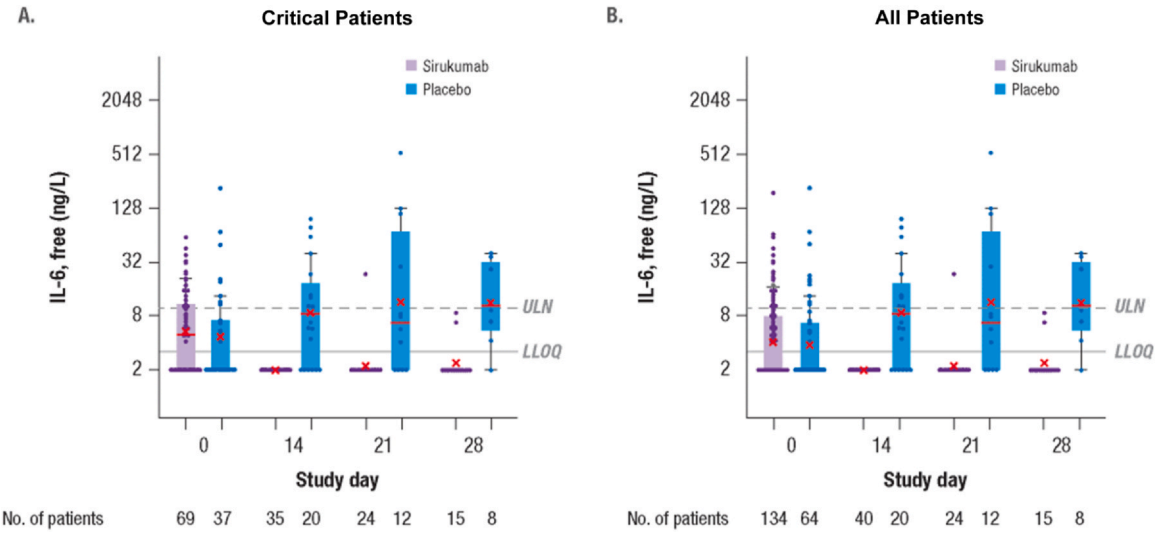

Fig. 2. Free IL-6 levels over time in (A) Critical and (B) All Patients treated with sirukumab or placebo. The dotted line represents the ULN (10 ng/L), and the solid line represents LLOQ (4 ng/L). X represents the geometric mean; horizontal bars indicate the median. IL-6, interleukin-6; LLOQ, lower limit of quantitation; ULN, upper limit of normal.

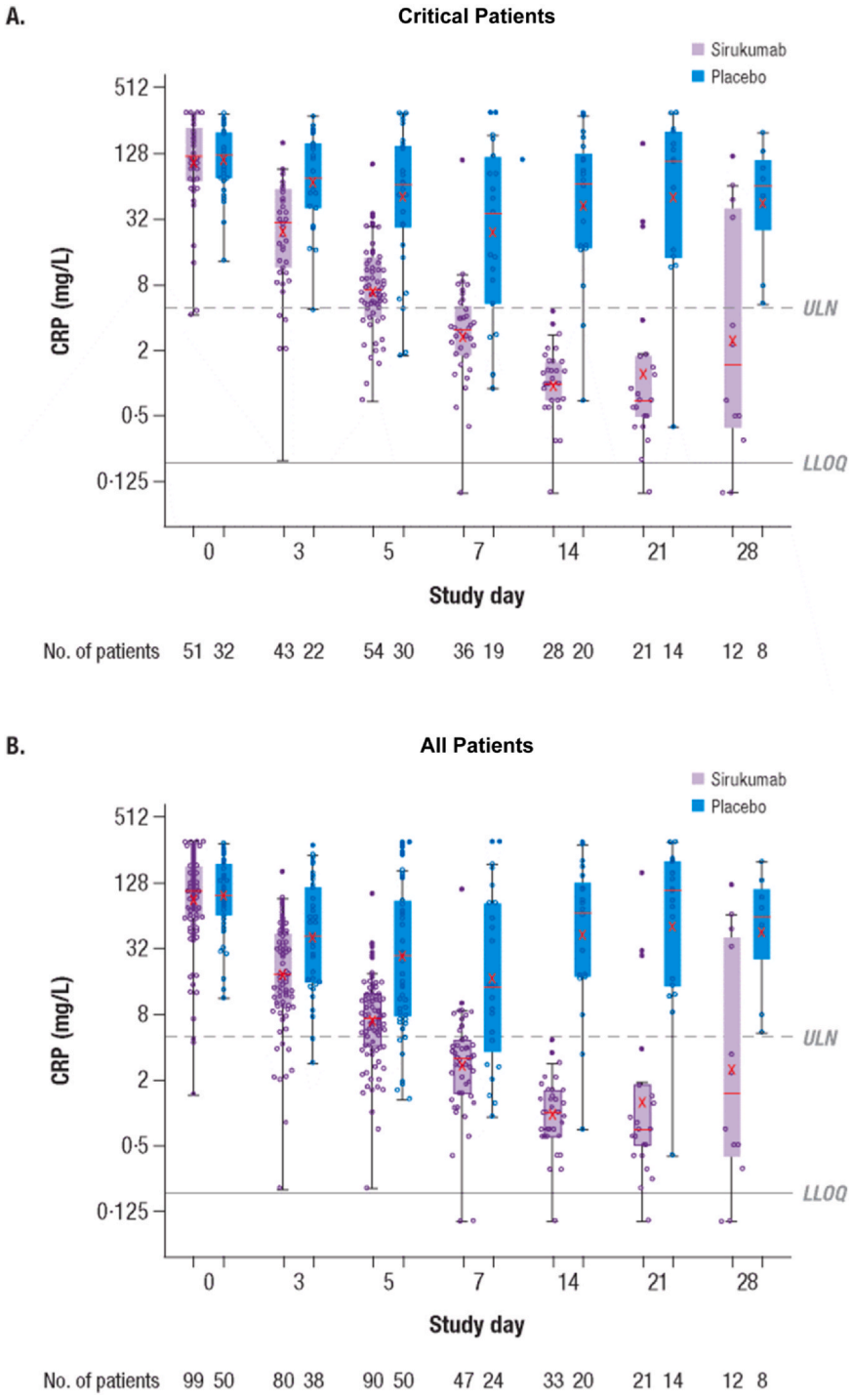

Fig. 3. CRP levels over time in (A) Critical and (B) All Patients treated with sirukumab or placebo. The dotted line represents the ULN (5 mg/L), and the solid line represents LLOQ (0·2 mg/L). X represents the geometric mean; horizontal bars indicate the median. CRP, C-reactive protein; LLOQ, lower limit of quantitation; ULN, upper limit of normal.

Safety

Rates of AEs up to Day 28 (treatment phase) are shown in Table 3. In the All Patients group up to Day 28, ≥1 AE was reported in 49·6% (69/139) and 52·9% (37/70) of those treated with sirukumab and placebo, respectively. Up to Day 28, 35 (25·2%) and 22 (31·4%) patients in the sirukumab and placebo groups, respectively, had serious AEs. Up to Day 28, 23 (16·5%) and 12 (17·1%) of patients treated with sirukumab and placebo, respectively, had infections (serious and nonserious).

During the follow-up phase through Week 16, 16 of 118 (13·6%) patients in the sirukumab group and seven of 57 (12·3%) patients in the placebo group had one or more AEs (Supplemental Table 3). Seven (5·9%) and three (5·3%) patients in the sirukumab and placebo groups, respectively, had serious AEs, and no infections were reported.

Discussion

This phase 2 study examined the efficacy and safety of the IL-6 antibody sirukumab in patients with confirmed severe or critical

Table 3
Summary of AEs during the treatment phase of the study (2:1; sirukumab:placebo).

	All Patients	
	Sirukumab + SOC (N = 139)	Placebo + SOC (N = 70)
AE	69 (49·6)	37 (52·9)
AE related to study drug	16 (11·5)	5 (7·1)
AE leading to death	20 (14·4)	14 (20·0)
Serious AE	35 (25·2)	22 (31·4)
Grade ≥3 AE	36 (25·9)	23 (32·9)
Grade ≥3 AE related to study drug	6 (4·3)	1 (1·4)
AE of special interest[a]	28 (20·1)	13 (18·6)
AE of special interest[a] related to study drug	12 (8·6)	3 (4·3)
Infections and infestations	23 (16·5)	12 (17·1)

Data are n (%). The treatment phase starts at the date/time of study drug administration and ends at the Day 28 visit or phone call (or, if earlier, at the date of discontinuation or death).
AE, adverse event; SOC, standard of care.
[a] Per investigators' assessment. AEs of special interest included serious infections, hypersensitivity, haematologic events, and liver enzymes.

COVID-19. The primary objective was not met: the difference in time to sustained clinical improvement of at least two categories up to Day 28 for sirukumab plus SOC compared with placebo plus SOC in patients with critical COVID-19 was not statistically significant. Overall, sirukumab was generally safe and well tolerated; the safety findings were consistent with the known safety profile of sirukumab.[24,25]

Several meta-analyses have reported decreased mortality and improved outcomes with IL-6 pathway inhibitors acting at the receptor level (e.g., anti-IL6–receptor mAbs) in critically ill patients with COVID-19. However, it is important to note that the underlying individual trials of these meta-analyses showed mixed results.[17] A prospective observational cohort study of siltuximab, a different anti-IL-6 mAb, suggested lower 30-day mortality in COVID-19 patients compared with propensity-score matched controls (HR, 0·46; 95% CI, 0·22–0·97).[26] The RECOVERY study also showed lower mortality in hospitalised patients who received tocilizumab plus SOC.[14] In the REMAP-CAP study, in-hospital mortality rates were 28% (98/350) in the tocilizumab plus SOC group, 22% (10/45) in the sarilumab plus SOC group, and 36% (142/397) in the SOC only group.[15] Negative results include those from the phase 3 REMDACTA trial, which found no differences between tocilizumab and placebo for hospitalisation or mortality at Day 28.[27] A phase 2/3 trial of sarilumab showed no significant differences between sarilumab and placebo for death in hospitalised patients with COVID-19.[16] Finally, in the CORIMUNO-SARI-1 trial, sarilumab demonstrated no benefit with respect to reducing the need for ventilation or improving survival.[28] Taken together, our results combined with the results of meta-analyses that consider the body of clinical findings, the totality of evidence suggests a possible modest improvement in mortality for IL-6 pathway antagonist administration in selected patients hospitalised for COVID-19. Our study was powered to test and detect only large effect sizes. Nevertheless, our study provides unique, key insights that are only assessable by modulation upstream of the IL-6 receptor, as achieved here. Lack of a large effect size, despite prompt and profound reduction of circulating IL-6 levels following sirukumab administration, suggests that modulation of IL-6 pathway signalling is not as pivotal of a therapeutic strategy as was initially hypothesised.

Other potential reasons for our observations include that SOC/supportive care had improved as positive studies were reported, thereby reducing the impact of targeting the IL-6 pathway on outcomes in patients with COVID-19. The initial positive observations of clinical trials targeting the IL-6 pathway may no longer apply in contemporaneous settings as the biology and treatment of COVID-19 have evolved to include high use of corticosteroids for critical COVID-19. For example, in the RECOVERY study, 82% of patients received systemic corticosteroids in addition to tocilizumab.[14] At the time of the SISCO study, which enrolled patients from 7 March to 9 April 2020, best supportive care included antiviral therapy and hydroxychloroquine, with the latter subsequently understood to be ineffective. Corticosteroids were not permitted until 27 March 2020, and shortly after, subcutaneous prophylactic low molecular weight heparin was also permitted.[26] Although this trial was initiated early in the pandemic, the peak enrolment occurred when nearly 100% of patients received antivirals, corticosteroids, or anticoagulants, suggesting that there is still IL-6–related inflammation despite use of these three treatments. This finding is consistent with a Bayesian reanalysis of randomised controlled trials of patients who received corticosteroids and tocilizumab.[29]

Uniquely, our trial allows insight into IL-6 modulation by allowing direct measurement of free IL-6 not just at baseline, but in response to the therapy, unlike anti-IL-6–receptor mAbs that do not permit direct quantification of the extent of IL-6 blockade. Despite prompt and nearly complete IL-6 sequestration, time to sustained clinical improvement was not statistically different versus placebo. That said, although our results were not statistically significant, exploratory analysis of biomarker subgroups indicate that certain patients may be more likely to benefit from sirukumab treatment (manuscript submitted). Other studies have suggested that patients with higher CRP or IL-6 levels might show a greater response to IL-6 pathway inhibition. For example, the COVIDSTORM study only included patients with elevations in at least two inflammatory markers (IL-6 > 11.8 ng/L [2 × ULN]; ferritin > 300 mg/L in women or > 800 mg/L in men [2 × ULN]; D-dimer > 1.5 mg/L; or CRP > 40 mg/L).[30] In patients who received tocilizumab in COVIDSTORM, a significant reduction in median length of hospitalisation was observed for patients who received tocilizumab versus SOC.[30] Overall, CRP was elevated in our COVID-19 patient population, which is largely in line with previously published data, and decreased in response to treatment.[30,31] In the current study, baseline IL-6 levels were relatively low and lower than initially anticipated, but are similar to those reported in more recent studies in which corticosteroids were also part of SOC (median baseline IL-6 was 8 ng/L for no IL-6 blockade and 9 ng/L for IL-6 blockade compared with ~5 ng/L in this study).[31] The extent to which baseline levels of IL-6 influence response to IL-6 pathway blockade in severe or critical COVID-19 patients remains to be determined. Decreases in free IL-6 and CRP in patients with COVID-19 treated with sirukumab were expected and are in line with the known effects of sirukumab in rheumatoid arthritis.[32]

This study has several strengths and limitations. Limitations include the relatively modest sample size, as the trial was powered to detect large differences. Additional limitations include that most of the enrolled patients were male, and the study population had low racial diversity; approximately 80% of the enrolled patients were White. However, close to half of the patients enrolled were of Hispanic or Latino ethnicity. Furthermore, as this study was done prior to the wide availability of vaccines, the clinical relevance of sirukumab in the vaccinated or immune population is uncertain. Finally, we did not examine relative contributions of IL-6 classical (membrane-bound IL-6-receptor–mediated) and trans-signalling (soluble IL-6-receptor–mediated) as both would be blocked by sirukumab.[33]

Strengths include that the study design evolved to adjust to rapidly changing SOC guidelines for patients with critical or severe COVID-19. For example, patients were permitted to participate in a single-arm clinical trial with an antiviral drug with a demonstrated in vitro effect against SARS-CoV-2.

Uniquely, our trial allows insight into IL-6 modulation by allowing direct measurement of free circulating IL-6 not just at

baseline, but in response to the therapy, unlike anti-IL-6–receptor mAbs, which do not permit direct quantification of the extent of IL-6 blockade. Despite prompt and nearly complete IL-6 sequestration, clinical outcomes were not statistically different, questioning the prevailing hypothesis that IL-6 signalling is a key pathophysiologic and therapeutic pathway in COVID-19.

Conclusions

In this phase 2 study conducted in patients with critical COVID-19, although the reduction in the rate of mortality was in line with previous studies of IL-6 pathway inhibitors, the primary endpoint of shorter time to sustained clinical improvement was not statistically significant. Further studies examining sirukumab in patients with COVID-19 are not planned. A significant burden of COVID-19 persists in critically ill patients despite near complete sequestration of circulating IL-6, questioning the IL-6 hypothesis as a selective therapeutic target in critical COVID-19.

Funding

Janssen Research & Development, LLC.

Author contributions

Robert Gottlieb was a national coordinator and site investigator, and contributed to supervision, data acquisition, data interpretation, and writing of the original draft. Meredith Clement was a study site investigator and contributed resources. Paul Cook, Audra Deveikis, Kap Sum Foong, Philip Robinson, and Cedric W. Spak were study investigators. Jihad Slim was a study investigator and provided supervision. Annemie Buelens and Katleen Callewaert contributed to the statistical analysis. Sandra De Meyer contributed to the conceptualization, formal analysis, methodology, and supervision. Wai Ling Mo was the study operations central team leader. Inge Verbrugge contributed to the study design, data analysis and data interpretation. Liesbeth Van Wesenbeeck contributed to the Study design, data analysis, and data interpretation. Yanli Zhuang and Jason Chien contributed to the study design and data analysis. Magda Opsomer was the medical leader and contributed to the conceptualization, study design, methodology, data analysis, and supervision. Erika Van Landuyt was the study responsible physician.

All authors critically reviewed the manuscript for intellectual content. All authors had full access to the data and had final responsibility for the decision to submit for publication. Erika Van Landuyt and Robert L. Gottlieb directly accessed and verified the underlying data reported in the manuscript.

Data availability

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinicaltrials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Declaration of Competing Interest

Robert L. Gottlieb served as coordinating national principal investigator and as a consultant for this trial. He reports service on scientific advisory boards for AbbVie, AstraZeneca, Eli Lilly, Gilead Sciences, GSK, and Roche, and consulting via his institution for Kinevant Sciences, also related to COVID-19. Service on speakers bureau with Alnylam Pharmaceuticals and Pfizer, consultancy to Alnylam, research support from CareDx, and a gift-in-kind to his institution from Gilead Sciences to support NCT03383419 are also reported, all outside the submitted work. Meredith Clement has received research support (grants to institution) from Gilead Sciences and ViiV Healthcare, has served on advisory boards for Roche Diagnostics Corporation and ViiV Healthcare. Paul Cook is a PI for the following: NIH, Janssen, Gilead, ViiV, Seres, and Finch. Audra Deveikis, Kap Sum Foong, Philip Robinson, and Cedric W. Spak have nothing to declare. Jihad Slim serves on speakers bureaus for Gilead, ViiV, Merck, Janssen, AbbVie, and Thera. Katleen Callewaert is an employee of Janssen Pharmaceutica NV. Annemie Buelens, Sandra De Meyer, Liesbeth Van Wesenbeeck, and Erika Van Landuyt are employees of Janssen Pharmaceutica NV and own stock in Johnson & Johnson. Wai Ling Mo is an employee of Janssen-Cilag Limited. Inge Verbrugge and Magda Opsomer were employees of Janssen Pharmaceutica NV at the time of the study. Yanli Zhuang and Jacon Chien were employees of Janssen Research & Development, LLC at the time of the study.

Acknowledgements

The authors would like to acknowledge the patients who participated in this study and their families, as well as the staff members at the study sites, the data and safety monitoring committee, and the staff members involved in data collection and analyses. This study (ClinicalTrials.gov identifier: NCT04380961) was sponsored by Janssen Research & Development, LLC. Medical writing support was provided by Miranda Tradewell, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC.

The authors would also wish to acknowledge the following people: *Biomarkers*: Jeroen Aerssens, Marjolein Crabbe, Matthew Loza, Kim Thys, Linghua Zhou; *Compound Development Team Leaders*: Nando Bansal, Goedele de Smedt; *Central Monitoring*: Khiltee Beeharry, Jennifer Goewey, Joanna Lalewicz, Julian Ortiz; *Clinical*: Maria Beumont-Mauviel, Wassim Fares, Elizabeth (Liz) Hsia, Denny Kim, Isabelle Lonjon-Domanec, Liza O'Dowd; *Data Management*: Robbe Blarinckx, Amélie Cuny, Michèle Neeter, James Raine, Sheila Saunders, Gunasekaran Subramaniam, Ellen van Son, Jeanne Wagner; *Data Sciences*: Lilian Li, Kristopher Standish; *Drug supply*: Joerka Bendo, Eileen Brett, Andrew Mackay, Pratik Shah, Helen Stapleton and team; *Epidemiology*: Darmendra Ramcharran; *Feasibility*: Pinal Patel; *Global Medical Affairs*: Bryan Baugh, Kim Brown, Debra Israel, Dennis Rice and the team at Medical Science Liaisons, Ellen Sevenhans, Torunn Thingstad; *Global Clinical Trial Assistants*: Veronica Benitez, Montserrat Camacho, Enrique Chimal, Ana Lemus, Kathleen Marquez, Inge Scheys; *Immunology, Virology*: Navin Rao, Lotke Tambuyzer; *Independent Drug Monitoring*: Mathew Garvin and team of independent drug monitors, Tammy Nguyen; *Medical Writing*: Carla Clé , Fred Del Vecchio, Katrien Faes, Lara Lan, Nancy Van Aelst; *Operations Central Team*: Polan Chetty, Anna Duca, Lauren Elvanian, Valerie Joanny, Katie McFadden, Jeffrey Morales, Clark Musto, Sameer Nelugal, Molli Sandor and team, Linda Smets, Colleen Spicer, Barbara Uritz, Holly Veno, Chris Zizzamia; *Operations, US Local Team*: Heather Bartnek, Lynne Claye, Shannon Cunningham, Sarah Ellis, Laura Hawes, Barbara Isekenegbe, Lea Knapik, Tom Leeuwen, Dina Mangione, Brooke Miller, Rhiannon Rohrer, Miriam Rutz, Linda Smets, Kim Taylor, Liesbeth Versteeg-van Gent; *Pharmacology and Modelling*: Richard Hoetelmans, Weiron Wang, Jia Zhou; *Programming*: Srujana Anugu, Patrick De Locht, Keerthana Palwai, Lisa Varma; *Project Management*: Annemie Hendrickx, Greet Kauwenberghs, Ashley Kreiling, Rebecca Mack and project management team, Patricia Schel, An Van Eyken; *Regulatory Affairs*: Linda Barone, Melissa Calmann, Laura Curcio, Barbara Lenhart, Aileen Li, Alla Rhoge, Kiva Stewart, Chantal Verkleij, Hilde Walgraeve; *Safety*: Elena Bolshtyansky, David Paar; *Statistics*: Filip de Ridder, Ashish Kumar, Leen Slaets, Monika Peeters; and all other Janssen contributors, possibly inadvertently omitted here, for their contributions to this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106241.

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