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Original Article

Safety and efficacy of selective RIPK1 inhibitor SIR1-365 in hospitalized patients with severe COVID-19: A multicenter, randomized, double-blind, phase 1b trial

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ABSTRACT

Background: Receptor-interacting protein kinase 1 (RIPK1), a serine/threonine protein kinase, is mainly activated by pro-inflammatory cytokines and pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its activation could result in apoptosis, necroptosis, or inflammation. This study was conducted to evaluate the safety and efficacy of a potent and selective inhibitor of RIPK1, SIR1-365, in hospitalized patients with severe coronavirus disease 2019 (COVID-19).

Methods: This multicenter, randomized, double-blind, phase 1b study screened patients from December 18, 2020 until November 27, 2021. Adults hospitalized with severe COVID-19 (diagnosed ≤2 weeks before screening) were randomized 1:1 to receive oral placebo or SIR1-365 100 mg three times daily for ≤14 consecutive days, with standard-of-care. The primary objective was to evaluate SIR1-365 safety and tolerability. Secondary objectives included an assessment of SIR1-365 efficacy. Descriptive statistics were used to summarize safety. The study was not powered for efficacy testing. Relevant inferential statistical tests were used to aid interpretation of differences in clinical efficacy.

Results: Forty-five patients were randomized, 42 were treated. Eighteen patients experienced treatment-emergent adverse events (TEAEs) and 7 patients were ≥ grade 3. Fewer SIR1-365-treated *vs.* placebo-treated patients experienced TEAEs (30.4% *vs.* 57.9%) and serious TEAEs (13.0% *vs.* 26.3%) within 28 days of the first dose. There were no serious treatment-related TEAEs or deaths. Compare to placebo, SIR1-365 significantly increased arterial oxygenation from baseline to day 7 (least-squares mean change [standard error]: 109.4 [26.4] *vs.* -24.2 [23.6]; P=0.0095), significantly reduced hospitalization duration after treatment (mean±standard deviation: [4.7±3.7] days *vs.* [8.6±5.6] days; P=0.0145) and respiratory failure incidence (8.3% *vs.* 38.1%; two-sided P=0.0291) during the study, and numerically shortened the time to clinical improvement in World Health Organization ordinal scale (median: 5.0 days *vs.* 9.0 days, P=0.0766).

Conclusions: SIR1-365 was well tolerated and demonstrated a trend toward quicker recovery than placebo in hospitalized patients with severe COVID-19.

Trial Registration ClinicalTrials.gov number: NCT04622332

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Patients present with a wide range of disease severity from asymptomatic or mild, self-limiting respiratory tract illness to severe progressive pneumonia requiring hospitalization, multiorgan failure, and death.[2,3] For hospital-

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ized patients with severe COVID-19, the antiviral agent remdesivir, dexamethasone, and targeted anti-inflammatory agents are currently recommended.[4] This recommendation is based on the pathogenesis of COVID-19, which is thought to be driven by the replication of SARS-CoV-2 early in the disease course, followed by dysregulated immune response to viral infection later in the disease course.[4] The complex interplay between SARS-CoV-2 and host immune response activates multiple inflammatory pathways leading to hyperinflammation, cytokine storm, and consequently tissue damage.[5] The hyperinflammatory response induced by SARS-CoV-2 contributes to disease deterioration and death[6] and provides support for the use of anti-inflammatory therapy strategies, including dexamethasone and more targeted agents, to mitigate severe COVID-19.[5,7]

Interleukin (IL)-6R inhibitors tocilizumab and sarilumab and Janus kinase inhibitors baricitinib and tofacitinib are targeted anti-inflammatory agents that have been shown to ameliorate immune hyperactivation and are currently recommended as an adjunct to dexamethasone for certain severe COVID-19 patients with hypoxemia.[4] However, IL-6R inhibitors selectively inhibit the IL-6 pathway alone and have shown modest or no survival benefits in clinical trials of patients with severe COVID-19.[4] Janus kinase inhibitors have shown improved clinical outcomes among hospitalized patients with COVID-19, but are associated with an increased risk of respiratory tract infections.[4] Despite all the work done to date around the world, there is still no definitive treatment for COVID-19.

Receptor-interacting protein kinase 1 (RIPK1) is a serine/threonine protein kinase that is ubiquitously expressed in cells of most human tissues. Activation of the RIPK1 leads to either cell death or pro-inflammatory cytokine expression, both of which are closely associated with the pathogenesis of various human diseases.[8] RIPK1 can be activated by pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α or interferon-γ, as well as by pathogens including bacteria and viruses.[9] Recently, multiple studies have shown that RIPK1 is activated in patients with COVID-19, suggesting the involvement of RIPK1 in the pathogenesis of this disease.[10–14]

The most well-studied molecular mechanism of RIPK1 activation is via the TNF-α-mediated pathway. When TNF-α binds to its receptor TNFR1, RIPK1 regulates either the nuclear factor kappa B pathway that is “pro-survival” and kinase-independent or the apoptosis/necroptosis pathways that is “pro-death” and kinase dependent.[15] The determining factors of these two opposite mechanisms are the post-translational modification statuses of the RIPK1 protein, which include ubiquitination, phosphorylation, and proteolysis.[16] Humans bearing a point mutation at the D324 site of the RIPK1 protein that renders it non-cleavable by the protease caspase 8 suffer from severe inflammation, which suggests a detrimental consequence of RIPK1 activation in humans.[17,18]

Activation of RIPK1 has been demonstrated in the lung tissue and plasma of severe COVID-19 patients, cultured human lung organoids, and transgenic mice infected by SARS-CoV-2.[13,14,19,20] One study showed persistently elevated plasma concentrations of RIPK1 and other necroptosis-related proteins in patients with COVID-19 in the intensive care unit, compared with healthy controls.[19] Mechanistically, the RNA-dependent RNA polymerase of SARS-CoV-2 was found to directly interact with RIPK1 and promote its activation, which potentially facilitates SARS-CoV-2 viral propagation.[14] Inhibition of RIPK1 using multiple RIPK1 inhibitors prevented TNF-dependent inflammation in preclinical models[11,13,21–23] and reduced the viral load of SARS-CoV-2 in human lung organoids and transgenic mice.[14] Inhibiting RIPK1 activity therefore provides a potential new approach for the treatment of immune-mediated inflammatory diseases,[11] including COVID-19.[10,12–14,24]

SIR1-365 is a highly potent, selective, and metabolically stable allosteric kinase inhibitor of RIPK1.[25] In a systemic inflammatory response syndrome mice disease model, SIR1-365 efficiently reduced TNF-α-induced mortality and multiorgan damage.[25] A first-in-human dose-ranging study of SIR1-365 has demonstrated its safety, tolerability, and pharmacokinetics at doses up to 600 mg/day for 10 consecutive days in healthy volunteers (Unpublished results, Sironax Aus Pty Ltd. Sydney, Australia, a subsidiary of Sironax, Ltd.). Compared to selective IL-6R inhibitors, RIPK1 inhibitor SIR1-365 may be more advantageous to reduce the hyperinflammatory response in severe COVID-19. The present global phase 1b study was conducted to evaluate the safety and efficacy of SIR1-365 in hospitalized patients with severe COVID-19.

Methods

Study design

This phase 1b, randomized, double-blind, placebo-controlled study was conducted at nine study sites in Mexico, Pakistan, and the USA (ClinicalTrials.gov NCT04622332). All patients were randomized in a 1:1 ratio to receive placebo or SIR1-365 at 100 mg three times daily (TID) for 14 consecutive days or until hospital discharge, whichever occurred earlier. Treatment was administered orally either as intact tablets with water if the patient was able to swallow or as a disintegrated suspension form delivered via a nasogastric tube if the patient was unable to swallow. The dose of SIR1-365 100 mg TID was selected based on the results of the systemic inflammatory response syndrome mice disease model study[25] and pharmacokinetics data from the multiple ascending dose study in healthy volunteers (Supplementary material S1). All randomized patients received standard-of-care treatments for COVID-19 throughout the study.

The overall duration of the study was up to 35 days, including up to 7 days for screening, up to 14 days for treatment, and a follow-up visit (14±3) days after the last dose. The present analysis used data extracted at the database lock date of December 10, 2021, when all randomized patients had completed the study or discontinued the study earlier.

Randomization and masking

Randomization was generated using a centralized interactive response technology (Supplementary material S2) and stratified according to age group (<60 years or ≥60 years), dexamethasone use (yes or no), and remdesivir use (yes or no). Treatment assignment in the study was blinded to the investigators, patients, and sponsors.

Patients

Eligible patients were between 18 years and 80 years old and hospitalized due to clinical diagnosis of SARS-CoV-2 virus

infection as per World Health Organization (WHO) criteria within 2 weeks prior to screening, severe systemic COVID-19 signs and symptoms according to Food and Drug Administration guidelines,[26] and plasma C-reactive protein (CRP) levels >50 mg/L or 4 × upper limit of normal (ULN) range at screening. Symptoms suggestive of severe COVID-19 included any of the following: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath at rest, or respiratory distress. Clinical signs indicative of severe COVID-19 included any of the following: respiratory rate ≥30 breaths/min, heart rate ≥125 beats/min, oxygen saturation (SpO_2) ≤93.0% on room air, the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltration >50.0% on chest X-ray imaging.

Patients who required endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula, non-invasive positive pressure ventilation, extracorporeal membrane oxygenation, or clinical diagnosis of respiratory failure were excluded. Patients who had shock (defined by systolic blood pressure <90 mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressor), used chronic systemic corticosteroids within 2 weeks prior to screening, or received immunosuppressant or immunomodulatory drugs, including anti-cytokine therapies targeting TNF-α, IL-1, IL-6, interferon-β, or Bruton's tyrosine kinase, within 1 month prior to screening were also excluded. Full inclusion and exclusion criteria are listed in Supplementary material S3 and S4. Significant changes instituted in eligibility criteria and other study protocols during the course of the study are summarized in Supplementary material S5.

Study objectives and assessments

Since the safety, pharmacokinetics, and pharmacodynamics of SIR1-365 at multiple ascending doses have been demonstrated in the aforementioned study in healthy volunteers (Unpublished results, Sironax Aus Pty Ltd., a subsidiary of Sironax, Ltd.), this phase 1b study aimed to assess both the safety and preliminary efficacy of SIR1-365 in hospitalized patients with severe COVID-19. The primary objective was to evaluate the overall safety and tolerability of SIR1-365. The secondary clinical objectives included an assessment of the clinical efficacy of SIR1-365 and the effects of SIR1-365 on inflammatory biomarkers, including lymphocyte and neutrophil counts. The clinical efficacy of SIR1-365 was evaluated by change in the ratio of PaO_2/FiO_2 from baseline to days 7 and 14, change in the score of the WHO ordinal scale[27] from baseline to days 7, 14, and 28, and the proportion of patients with clinical improvement defined as a reduction of 2 points in the WHO ordinal scale, number of days hospitalized, and the proportion of patients who experienced respiratory failure during the study from baseline to day 28.

Safety was determined by monitoring the extent of exposure, treatment-emergent adverse events (TEAE), clinical laboratory values, vital signs, physical examinations, and 12-lead electrocardiogram.

PaO_2/FiO_2 ratio was evaluated by a blood gas analyzer at screening, within 30 min before dosing on day 1 as a baseline, and within 30 min after the second dose on days 7 and 14. The WHO ordinal scale, a 10-level ordered categorical scale,[27] was used to measure COVID-19 disease severity during the study. Days of hospitalization were recorded based on the date and time of the first dose of study treatment and hospital discharge (duration of hospitalization in days=the date of discharge - the date of the first dose of study treatment + 1). Respiratory failure was defined as a need for mechanical ventilation, extracorporeal membrane oxygenation, non-invasive ventilation, or high-flow nasal cannula oxygen delivery.

Statistical analysis

This was a safety study and was not powered to detect predefined differences in clinical efficacy. Sample size was determined empirically. A planned sample size of 30 patients per treatment group was considered sufficient to detect marked differences in the overall safety profile between treatment groups with a prespecified safety monitoring plan. Safety was assessed in the safety set, including all randomized patients who received at least one dose of placebo or SIR1-365. Efficacy analyses, including analysis of lymphocytes and neutrophils, were performed in the intent-to-treat (ITT) population that consisted of all randomized patients.

The extent of exposure to the study drug and TEAEs was summarized using descriptive statistics by the treatment group. TEAEs were coded using the Medical Dictionary for Regulatory Activities Version 23.0 or above, and the severity of TEAEs was graded based on the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. Although the study was not powered for hypothesis testing of differences in clinical efficacy, *P*-values were generated to aid interpretation in addition to confidence intervals (CIs) about the estimates. The least-squares (LS) mean change in PaO_2/FiO_2 ratio from baseline was compared between treatment groups using an analysis of covariance model with fixed effects for treatment and the baseline score as a continuous covariate, based on the "actual" data that were obtained on days 7 and 14/end of treatment (EOT) (*i.e.*, no imputation for missing data) and the last observation carried forward (LOCF) if data were missing on days 7 and 14. The change in the WHO ordinal scale from baseline was compared between groups using a non-parametric Wilcoxon rank sum test, with LOCF in case of missing data. Time to clinical improvement in the WHO ordinal scale and time to first time back to normal in neutrophil and lymphocyte counts were analyzed using a Cox proportional hazards model. Duration of hospitalization was analyzed using a one-way analysis of variance model with a single term for treatment. The proportion of patients with respiratory failure was compared between groups using a two-sided Fisher's exact test. All statistical analyses were performed using SAS software Version 9.4 or higher. CONSORT guidelines are followed in this report.[28]

Results

Patients

From December 18, 2020, to November 27, 2021, 62 patients from Mexico, Pakistan, and the USA were screened; 45 patients were randomized to receive placebo (*n*=21) or SIR1-365 (*n*=24) and were included in the efficacy analysis (Figure 1). Two patients in the placebo group and 1 patient in the SIR1-

365 group were randomized but not treated; 42 patients received the assigned treatment and were included in the safety analysis. Four patients in each treatment group discontinued the study treatment. Reasons for discontinuation of the study treatment in the SIR1-365 group included withdrawal of consent by three patients and investigator decision for one patient. In the placebo group, two patients discontinued due to adverse events, one patient due to protocol deviation, and one patient based on investigator decision. All 34 patients (75.6%) who completed the study treatment also completed the study (Figure 1).

Treatment groups were generally balanced at baseline (Table 1). The median age of patients was 46 years; 26.2% were ≥60 years; 69.0% of patients were men; and most (57.1%) were either Asian or American Indian/Alaska Native. Almost all patients (97.6%) had used dexamethasone with or without remdesivir for COVID-19 treatment at study entry (Table 1).

Safety

Among the 42 patients who received study treatment, the median duration of exposure was 4.0 days (range: 2–14 days) for the placebo group and 2.3 days (range: 1–14 days) for the SIR1-365 group. The percentage of patients with ≥1 TEAE within 28 days of the first dose of study treatment was higher in the placebo group (57.9%) than in the SIR1-365 group (30.4%) (Table 2). The TEAEs that occurred in more than one patient included alanine aminotransferase (ALT) increased (15.8% and 4.3% of patients in the placebo and SIR1-365 groups, respectively), aspartate aminotransferase (AST) increased (10.5% and 4.3%), pulmonary embolism (5.3% and 4.3%), fungal skin infection (5.3% and 4.3%), and headache (5.3% and 4.3%). The majority of TEAEs were mild or moderate (grade 1 or 2); five patients (26.3%) in the placebo group and two patients (8.7%) in the SIR1-365 group had TEAEs that were ≥ grade 3. Two patients (both in the placebo group) discontinued study treatment due to TEAE (Table 2).

The percentage of patients who experienced serious TEAEs within 28 days of the first dose of study treatment was also higher in the placebo group (26.3%) than in the SIR1-365 group (13.0%) (Table 2). In the placebo group, five patients had seven serious TEAEs, pulmonary embolism, acute respiratory failure, hemoptysis, respiratory distress, respiratory failure, acute myocardial infarction, and pneumonia, all with onset ≤7 days after the first dose of placebo. In the SIR1-365 group, three patients had three serious TEAEs, pulmonary embolism with onset ≤7 days of the first dose of SIR1-365, and neck pain and encephalopathy with onset between 14 days and 28 days of the first dose of SIR1-365. None of the serious TEAEs in the study was considered related to study treatment by the investigators. There were no deaths reported in the study.

Three patients (7.1%) experienced four treatment-related TEAEs, all of which occurred ≤7 days after the first dose of study treatment. One patient in the placebo group had a treatment-related TEAE of ALT increased. Two patients in the SIR1-365 group had three treatment-related TEAEs: hypotension and orthostatic hypotension in one patient and paresthesia oral in the other patient. All treatment-related TEAEs were mild or moderate (Table 2).

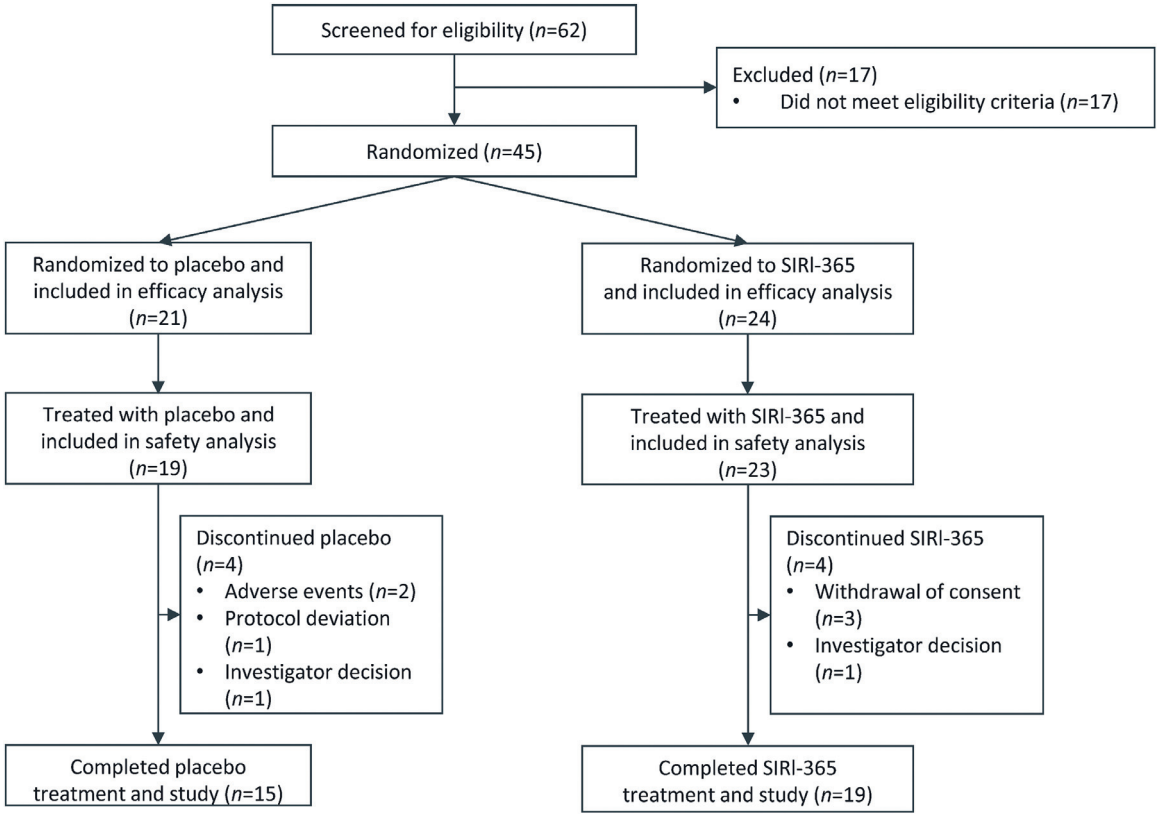

Figure 1. Patient disposition.

Table 1
Demographic and baseline characteristics in the safety set.

Items	Placebo (*n*=19)	SIR1-365 (*n*=23)	Total (*n*=42)
Age (years)*	46 (23–76)	45 (26–73)	46 (23–76)
Age ≥60 years	4 (21.1)	7 (30.4)	11 (26.2)
Sex			
Male	14 (73.7)	15 (65.2)	29 (69.0)
Female	5 (26.3)	8 (34.8)	13 (31.0)
Race			
White	3 (15.8)	6 (26.1)	9 (21.4)
Black or African American	1 (5.3)	1 (4.3)	2 (4.8)
Asian	4 (21.1)	6 (26.1)	10 (23.8)
American Indian or Alaska Native	6 (31.6)	8 (34.8)	14 (33.3)
Multiple races†	1 (5.3)	0	1 (2.4)
Not reported	4 (21.1)	2 (8.7)	6 (14.3)
Body mass index (kg/m^2)	30.5 (21.8–47.6)	27.8 (22.5–54.4)	28.5 (21.8–54.4)
Country			
Mexico	11 (57.9)	10 (43.5)	21 (46.7)
Pakistan	4 (21.1)	6 (26.1)	11 (24.4)
USA	4 (21.1)	7 (30.4)	13 (28.9)
Days of hospitalization before study treatment			
0	1 (5.3)	2 (8.7)	3 (7.1)
1	6 (31.6)	8 (34.8)	14 (33.3)
2	7 (36.8)	9 (39.1)	16 (38.1)
3	5 (26.3)	4 (17.4)	9 (21.4)
Dexamethasone or remdesivir use at study entry	19 (100)	22 (95.7)	41 (97.6)
Dexamethasone only	14 (73.7)	15 (65.2)	29 (69.0)
Remdesivir only	0	0	0
Both	5 (26.3)	7 (30.4)	12 (28.6)

Data are expressed as median (range) or *n* (%).
* Age at date of informed consent.
† Patient checked more than one race option.

Table 2
Adverse events in the safety set.

TEAEs	Placebo (*n*=19)	SIR1-365 (*n*=23)
TEAE	11 (57.9)	7 (30.4)
Grade ≥3 TEAE	5 (26.3)	2 (8.7)
TEAE occurring in >1 patient		
ALT increased	3 (15.8)	1 (4.3)
AST increased	2 (10.5)	1 (4.3)
Pulmonary embolism	1 (5.3)	1 (4.3)
Fungal skin infection	1 (5.3)	1 (4.3)
Headache	1 (5.3)	1 (4.3)
Serious TEAE	5 (26.3)	3 (13.0)
Pulmonary embolism	1 (5.3)	1 (4.0)
Acute respiratory failure	1 (5.3)	0
Hemoptysis	1 (5.3)	0
Respiratory distress	1 (5.3)	0
Respiratory failure	1 (5.3)	0
Acute myocardial infarction	1 (5.3)	0
Pneumonia	1 (5.3)	0
Neck pain	0	1 (4.3)
Encephalopathy	0	1 (4.3)
TEAE leading to treatment discontinuation	2 (10.5)	0
Respiratory failure	1 (5.3)	0
Acute myocardial infarction	1 (5.3)	0
Treatment-related TEAE	1 (5.3)	2 (8.7)
ALT increased	1 (5.3)	0
Hypotension	0	1 (4.3)
Orthostatic hypotension	0	1 (4.3)
Paresthesia oral	0	1 (4.3)
Serious treatment-related TEAE	0	0
Death	0	0

Data are expressed as *n* (%).
TEAEs were defined as adverse events that occurred and existing adverse events that worsened after the first dose of the study drug. Treatment-related TEAEs were those reported as "definite," "probable," or "possible," and not related adverse events (AEs) were reported as "unlikely" or "unrelated." TEAEs with a missing relationship were considered related to the study drug. Each patient might report more than one event; patients reporting more than 1 event per reporting category were counted only once for the patient count.
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TEAE: Treatment-emergent adverse event.

Efficacy

Preliminary efficacy analyses revealed clinical benefit at early time points in patients who received SIR1-365 *vs*. placebo. The actual LS change from baseline to day 7 in PaO_2/FiO_2 ratio, an index of arterial oxygenation, was significantly greater in the SIR1-365 group than in the placebo group (mean [standard error: 109.4 [26.4] *vs*. −24.2 [23.6], *P*=0.0095). These day 7 PaO_2/FiO_2 results were based on the actual data from only five patients in the placebo group and four patients in the SIR1-365 group. The mean change from baseline to day 7 in PaO_2/FiO_2 ratio based on the LOCF data and the mean change from baseline to day 14 in PaO_2/FiO_2 ratio (actual or LOCF data) was not different between SIR1-365 and placebo (Table 3).

The distribution of the WHO ordinal scale classification showed a trend that SIR1-365 increased the percentage of patients with ambulatory mild disease and decreased the percentages of hospitalized patients with moderate or severe disease, compared with placebo (Figure 2). The trend of reduced disease severity or improved recovery with SIR1-365 treatment *vs*. placebo was most apparent on day 7 but also observed on day 14/EOT (Figure 2). The mean±standard deviation change from baseline to day 7 (LOCF) in the WHO ordinal scale was numerically greater in the SIR1-365 group than in the placebo group ([−1.6±1.2] *vs*. [−0.6±2.1], *P*=0.1167); the mean change from baseline to days 14 and 28 in WHO ordinal scale was similar between the two groups (Table 4).

Numerically more patients in the SIR1-365 group *vs*. the placebo group exhibited clinical improvement, defined as a reduction of at least two points in the WHO ordinal scale, from baseline to day 28 or EOS (85.7% *vs*. 84.2%), from baseline up to day 7 (71.4% *vs*. 36.8%), and from baseline up to day 14/EOT (90.0% *vs*. 75.0%). The median time to clinical improvement trended shorter in the SIR1-365 group than

Table 3
Clinical outcomes of PaO_2/FiO_2 ratio in the ITT set.

PaO_2/FiO_2 ratio	Placebo (n=21)		SIR1-365 (n=24)		Difference *vs.* placebo (95% CI)	*P*-value
	n	Change of PaO_2/FiO_2 ratio, LS mean (SE)	n	Change of PaO_2/FiO_2 ratio, LS mean (SE)		
From baseline to day 7 (actual)*	5	−24.2 (23.6)	4	109.4 (26.4)	133.6 (46.4 to 220.8)	0.0095
From baseline to day 14/EOT (actual)*	12	109.2 (21.9)	16	87.8 (19.0)	−21.5 (−81.3 to 38.3)	0.4661
From baseline to day 7 (LOCF)*	12	65.9 (29.2)	16	88.8 (25.3)	22.8 (−56.8 to 102.5)	0.5600
From baseline to day 14 (LOCF)*	5	87.2 (16.2)	4	96.0 (18.1)	8.8 (−51.0 to 68.6)	0.7320

* Analysis of the covariance model was used to estimate LS means, differences *vs.* placebo, and corresponding SEs, CIs, and *P*-values. The "actual" data summarized assessments that occurred on days 7 and 14/EOT. In case of missing data, the last observation prior to day 7 (excluding baseline) was carried forward to day 7, corresponding to day 7 (LOCF); the last observation after day 7 and prior to day 14 was carried forward to day 14, corresponding to day 14 (LOCF).CIs: Confidence intervals; EOT: End of treatment or early discontinuation; ITT: Intent-to-treat; LOCF: Last observation carried forward; LS: Least-squares; PaO_2/FiO_2: Partial pressure of oxygen/fraction of inspired oxygen; SEs: Standard errors.

that in the placebo group (5.0 days *vs.* 9.0 days, hazard ratio [HR]=1.8511, *P*=0.0766).

The duration of hospitalization after treatment up to day 28/end of the study was significantly shorter in the SIR1-365 group than in the placebo group ([4.7±3.7] days *vs.* [8.6±5.6] days, *P*=0.0145). Fewer patients in the SIR1-365 group (two patients [8.3%]) than in the placebo group (eight patients [38.1%]) experienced respiratory failure during the study (two-sided *P*=0.0291). Furthermore, no patients in the SIR1-365 group and two patients (9.5%) in the placebo group required mechanical ventilation, and two patients (8.3%) in the SIR1-365 group and seven patients (33.3%) in the placebo group required high-flow nasal cannula oxygen delivery during the study.

Biomarker analysis

Analysis of lymphocytes and neutrophils showed numerically shorter time to recovery for patients in the SIR1-365 group *vs.* those in the placebo group, as indicated by the reduced number of days between study treatment administration and the first time neutrophil counts (median of 1.8 days *vs.* 20.1 days; HR=2.2781, 95% confidence interval: 0.7522 to 6.8992, *P*=0.1453) and lymphocyte counts (median of 3.6 days *vs.* 20.1 days; HR=2.4980, 95% confidence interval: 0.9088 to 6.8665, *P*=0.0760) back to normal.

Discussion

This is the study that demonstrated the safety and preliminary efficacy of an RIPK1 inhibitor in patients with COVID-19. Administration of SIR1-365 100 mg TID for up to 14 consecutive days was well tolerated in hospitalized patients with severe COVID-19. Most TEAEs were mild or moderate and there were no serious treatment-related TEAEs in the study. Fewer patients in the SIR1-365 group experienced TEAEs and serious TEAEs than those in the placebo group. The preliminary effi-

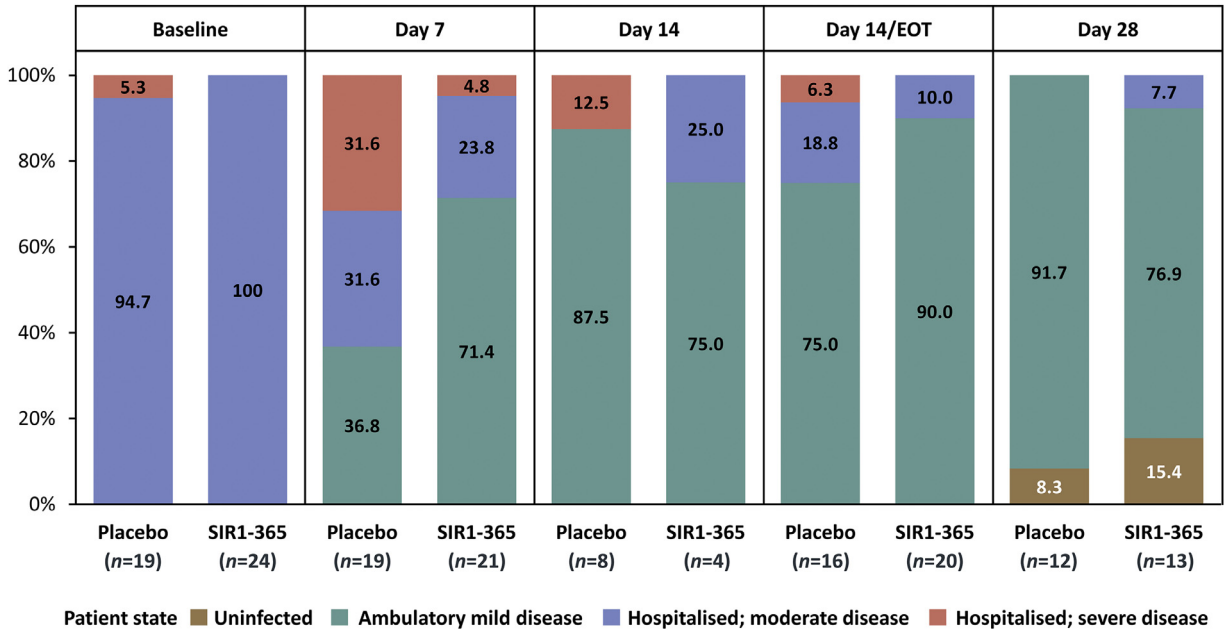

Figure 2. Stacked bar chart for WHO ordinal scale classification by visit and treatment (LOCF) in the ITT set. Baseline was the last non-missing value collected prior to the first dose of study drug. Percentages were calculated relative to the number of patients with data at each visit. In case of missing data, the last observation prior to day 7 (excluding baseline) was carried forward to day 7; the last observation after day 7 and prior to day 14 was carried forward to day 14; the last observation after day 14 was carried forward to day 28. The non-imputed values collected at the day 14/EOT visit were also included for comparative purposes.
EOT: End of treatment or early discontinuation; ITT: Intent-to-treat; LOCF: Last observation carried forward; WHO: World Health Organization.

Table 4
Clinical outcomes of WHO ordinal scale in the ITT set.

WHO ordinal scale	Placebo (n=21)			SIR1-365 (n=24)			P-value
	n	Mean ± SD change	Mean ± SD percentage change	n	Mean ± SD change	Mean ± SD percentage change	
Change from baseline to day 7 (LOCF)*	19	−0.6 ± 2.1	−12.6 ± 41.2	21	−1.6 ± 1.2	−33.8 ± 26.7	0.1167
Change from baseline to day 14 (LOCF)*	8	−2.1 ± 1.1	−42.5 ± 22.5	4	−1.8 ± 1.3	−35.0 ± 25.2	0.9111
Change from baseline to day 28 (LOCF)*	12	−3.2 ± 0.9	−64.2 ± 17.8	13	−3.4 ± 1.3	−69.6 ± 25.7	0.3904

* Exact two-sided P-values were obtained from a non-parametric Wilcoxon rank sum test to compare the change from baseline. In case of missing data, the last observation prior to day 7 (excluding baseline) was carried forward to day 7, corresponding to day 7 (LOCF); the last observation after day 7 and prior to day 14 was carried forward to day 14, corresponding to day 14 (LOCF); and the last observation after day 14 and before day 28 was carried forward to day 28, corresponding to day 28 (LOCF).ITT: Intent-to-treat; LOCF: Last observation carried forward; SD: Standard deviation; WHO: World Health Organization.

cacy analyses showed a trend in clinical benefit of SIR1-365 *vs*. placebo in severe hospitalized patients who received standard-of-care treatment, including greater change from baseline in oxygenation on day 7, faster reduction in the WHO ordinal scale, quicker recovery of neutrophils and lymphocytes, decreased duration of hospitalization, and reduced incidence of respiratory failure.

No unexpected safety signals were observed with SIR1-365 treatment in the present study of hospitalized patients with severe COVID-19. A lower proportion of patients in the SIR1-365 group reported TEAEs and serious TEAEs than those in the placebo group. Because many of the reported TEAEs and serious TEAEs were related to COVID-19 progression, the lower incidence of adverse events in the SIR1-365 groups *vs*. the placebo group may be partially attributed to the efficacy for SIR1-365. The present study, representative of phase 1 studies, included a limited number of patients; nevertheless, the safety data suggested that overall SIR1-365 had a favorable safety profile and was well tolerated.

Because of the important role of RIPK1 in inflammation[15,17,18,29,30] and pathogenesis of COVID-19,[10,12–14,19,20] RIPK1 inhibitors have been postulated to reduce inflammation and provide therapeutic benefit for patients with hyperinflammatory diseases,[11] including COVID-19.[10,12–14,24] A previous phase 1b study evaluated the effect of a different RIPK1 inhibitor, SAR443122, in patients with severe COVID-19. SAR443122 was considered safe and well tolerated. The percentage of patients with infections was higher in the placebo group (5/20; 25.0%) than that in the SAR443122 group (4/47; 8.5%). However, no significant differences were detected in any of the efficacy or biomarker endpoints between SAR443122 and placebo after up to 14 days of treatment.[31] The median time for ≥2-point improvement in a 7-point ordinal scale was 8 days with SAR443122 *vs*. 10 days with placebo (P=0.3770), the mean number of ventilator free days was 26.0 days with SAR443122 *vs*. 23.4 days with placebo, and the difference between SAR443122 and placebo in the change from baseline to day 7 in the ratio of saturated oxygen to FiO_2 was positive at 25.24.[31]

The present study results provided the evidence that an RIPK1 inhibitor, SIR1-365, might have clinical benefit at early timepoints to speed up the recovery process in hospitalized patients with severe COVID-19. Compared with placebo, SIR1-365 treatment significantly increased PaO_2/FiO_2 ratio or arterial oxygenation from baseline on day 7 based on the actual data. However, this result must be interpreted with caution as day 7 actual data were from a small number of patients since most patients had recovered from the disease and discharged from hospital before day 7. No between-group difference in arterial oxygenation was found on day 7 based on the LOCF data or on day 14/EOT based on either the actual or LOCF data. The LOCF data on day 7 were complicated by the fact that some patients, especially SIR1-365-treated patients, who had quick disease recovery and were discharged before day 7 were included in the analysis. On day 14/EOT, the between-group difference in arterial oxygenation was not expected since all patients had recovered from the disease when discharged from hospital. Consistent with the improvement of actual PaO_2/FiO_2 ratio on day 7, SIR1-365, compared with placebo, significantly decreased the proportion of patients who experienced respiratory failure during the study. For other efficacy measurements, SIR1-365 treatment showed a trend to reduce the WHO ordinal scale faster and greater than placebo. In addition, SIR1-365 significantly reduced the mean duration of hospitalization after treatment compared with placebo. A quicker recovery was also evidenced by numerically shorter time back to normal in neutrophil and lymphocyte counts. The shorter duration of treatment exposure in the SIR1-365 group *vs*. the placebo group serves as additional support for the efficacy of SIR1-365. As patients in both groups received the standard-of-care treatment for COVID-19 and patients could be discharged early based on the investigator's assessment, the shorter duration of exposure in the SIR1-365 group suggests that SIR1-365 may enable a quicker recovery and prohibit disease progression in hospitalized patients with severe COVID-19.

This study had several limitations. First, its sample size was small. The planned sample size was 60 patients, but only 45 patients were randomized in the study. Due to the high vaccination rate and the quickly changing epidemiology of SARS-CoV-2, hospitalized patients with severe COVID-19 were reduced during the trial's scheduled recruitment period and the planned number of patients could not be recruited. However, as the study results have shown, 45 patients seemed sufficient for a preliminary assessment of the safety and efficacy of SIR1-365. Despite the limited number of patients, the efficacy results were consistent across all measurements. Second, all patients received standard-of-care treatments for COVID-19 throughout the study, which may have obscured some between-group differences in study variables. However, it was necessary and only ethical to allow standard-of-care treatments for a disease that is associated with a high mortality rate[3] and has multiple treatment options available.[4] Third, this study was not powered to test predefined differences in secondary objectives of clinical efficacy or biomarkers and P-values could only be used to aid inter-

pretation of the effect estimates. Despite these limitations, the preliminary efficacy results showed a promising early benefit of SIR1-365 in patients with severe COVID-19.

Conclusions

Among hospitalized patients with severe COVID-19, SIR1-365 was well tolerated at 100 mg TID for up to 14 consecutive days. A trend toward a quicker recovery was observed with SIR1-365 *vs*. placebo, as demonstrated by increase in oxygenation and reduction in WHO ordinal scale, and decreased hospitalization duration and respiratory failure incidence. These results provide support for further development of RIPK1 inhibitor SIR1-365 for the treatment of hyperinflammatory diseases.

CRediT Authorship Contribution Statement

Norberto Chavez-Tapia: Writing – review & editing, Supervision, Project administration. **Muneeba Ahsan Sayeed:** Writing – review & editing, Supervision, Project administration, Data curation. **Shobha Luxmi:** Writing – review & editing, Supervision, Project administration, Data curation. **Douglas J. Kasper:** Writing – review & editing, Supervision, Project administration, Data curation. **Fenchao Xue:** Writing – review & editing, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Yang Shen:** Writing – review & editing, Data curation, Conceptualization. **Weiliang Fan:** Writing – review & editing, Data curation, Conceptualization. **Wei Yuan:** Writing – review & editing, Data curation, Conceptualization. **Bin Du:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

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Ethics Statement

The trial was approved by the Advarra institutional review boards at the participating sites on August 31, 2020, and conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization, the Declaration of Helsinki, and applicable local regulations. All patients provided written informed consent before study enrollment.

Conflict of Interest

Norberto Chavez-Tapia and Bin Du have performed clinical trial contract work done at industry-related remuneration with no further incentives for Sironax USA, Inc. Norberto Chavez-Tapia has also consulted with and/or received funding from Senosiain, Novartis, and MSD. Fenchao Xue, Yang Shen, Weiliang Fan, and Wei Yuan are employed by Sironax USA, Inc. Muneeba Ahsan Sayeed, Shobha Luxmi, and Douglas J. Kasper have nothing to disclose.

Data Availability

On request and subject to certain criteria and exceptions, Sironax USA, Inc., a Subsidiary of Sironax, Ltd., will consider requests for study protocol, statistical analysis plan, individual deidentified participant data, and data dictionary.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.07.003.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33. doi:10.1056/NEJMoa2001017.
[2] Berlin DA, Gulick RM, Martinez FJ. Severe COVID-19. N Engl J Med 2020;383(25):2451–60. doi:10.1056/NEJMcp2009575.
[3] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–42. doi:10.1001/jama.2020.2648.
[4] Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]. Bethesda (MD): National Institutes of Health (US); 2021 Apr 21-2024 Feb 29. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570371/[Last accessed on February 15, 2024].
[5] Tan LY, Komarasamy TV, Rmt Balasubramaniam VR. Hyperinflammatory immune response and COVID-19: a double edged sword. Front Immunol 2021;12:742941. doi:10.3389/fimmu.2021.742941.
[6] Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol 2021;191(1):4–17. doi:10.1016/j.ajpath.2020.08.009.
[7] Choi H, Shin EC. Hyper-inflammatory responses in COVID-19 and anti-inflammatory therapeutic approaches. BMB Rep 2022;55(1):11–19. doi:10.5483/BMBRep.2022.55.1.152.
[8] Degterev A, Ofengeim D, Yuan J. Targeting RIPK1 for the treatment of human diseases. Proc Natl Acad Sci USA 2019;116(20):9714–22. doi:10.1073/pnas.1901179116.
[9] Vanlangenakker N, Vanden Berghe T, Vandenabeele P. Many stimuli pull the necrotic trigger, an overview. Cell Death Differ 2012;19(1):75–86. doi:10.1038/cdd.2011.164.
[10] Cao L, Mu W. Necrostatin-1 and necroptosis inhibition: pathophysiology and therapeutic implications. Pharmacol Res 2021;163:105297. doi:10.1016/j.phrs.2020.105297.
[11] Harris PA. Inhibitors of RIP1 kinase: a patent review (2016-present). Expert Opin Ther Pat 2021;31(2):137–51. doi:10.1080/13543776.2021.1854729.
[12] Newton K, Dixit VM, Kayagaki N. Dying cells fan the flames of inflammation. Science 2021;374(6571):1076–80. doi:10.1126/science.abi5934.
[13] Riebeling T, Jamal K, Wilson R, Kolbrink B, von Samson-Himmelstjerna FA, Moerke C, et al. Primidone blocks RIPK1-driven cell death and inflammation. Cell Death Differ 2021;28(5):1610–26. doi:10.1038/s41418-020-00690-y.
[14] Xu G, Li Y, Zhang S, Peng H, Wang Y, Li D, et al. SARS-CoV-2 promotes RIPK1 activation to facilitate viral propagation. Cell Res 2021;31(12):1230–43. doi:10.1038/s41422-021-00578-7.
[15] Christofferson DE, Li Y, Yuan J. Control of life-or-death decisions by RIP1 kinase. Annu Rev Physiol 2014;76:129–50. doi:10.1146/annurev-physiol-021113-170259.
[16] Wang Q, Fan D, Xia Y, Ye Q, Xi X, Zhang G, et al. The latest information on the RIPK1 post-translational modifications and functions. Biomed Pharmacother 2021;142:112082. doi:10.1016/j.biopha.2021.112082.
[17] Lalaoui N, Boyden SE, Oda H, Wood GM, Stone DL, Chau D, et al. Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. Nature 2020;577(7788):103–8. doi:10.1038/s41586-019-1828-5.
[18] Tao P, Sun J, Wu Z, Wang S, Wang J, Li W, et al. A dominant autoinflammatory disease caused by non-cleavable variants of RIPK1. Nature 2020;577(7788):109–14. doi:10.1038/s41586-019-1830-y.
[19] Ruskowski K, Neb H, Talbot SR, Choorapoikayil S, Adam EH, von Knethen A, et al. Persistently elevated plasma concentrations of RIPK3, MLKL, HMGB1, and RIPK1 in patients with COVID-19 in the intensive care unit. Am J Respir Cell Mol Biol 2022;67(3):405–8. doi:10.1165/rcmb.2022-0039LE.

[20] Schweizer TA, Mairpady Shambat S, Vulin C, Hoeller S, Acevedo C, Huemer M, et al. Blunted sFasL signalling exacerbates TNF-driven neutrophil necroptosis in critically ill COVID-19 patients. Clin Transl Immunology 2021;10(12):e1357. doi:10.1002/cti2.1357.
[21] Berger SB, Harris P, Nagilla R, Kasparcova V, Hoffman S, Swift B, et al. Characterization of GSK'963: a structurally distinct, potent and selective inhibitor of RIP1 kinase. Cell Death Discov 2015;1:15009. doi:10.1038/cddiscovery.2015.9.
[22] Berger SB, Kasparcova V, Hoffman S, Swift B, Dare L, Schaeffer M, et al. Cutting edge: RIP1 kinase activity is dispensable for normal development but is a key regulator of inflammation in SHARPIN-deficient mice. J Immunol 2014;192(12):5476–80. doi:10.4049/jimmunol.1400499.
[23] Weisel K, Berger S, Thorn K, Taylor PC, Peterfy C, Siddall H, et al. A randomized, placebo-controlled experimental medicine study of RIPK1 inhibitor GSK2982772 in patients with moderate to severe rheumatoid arthritis. Arthritis Res Ther 2021;23(1):85. doi:10.1186/s13075-021-02468-0.
[24] Wei X, Pan C, Zhang X, Zhang W. Total network controllability analysis discovers explainable drugs for COVID-19 treatment. Biol Direct 2023;18(1):55. doi:10.1186/s13062-023-00410-9.
[25] Ren Y, Su Y, Sun L, He S, Meng L, Liao D, et al. Discovery of a highly potent, selective, and metabolically stable inhibitor of receptor-interacting protein 1 (RIP1) for the treatment of systemic inflammatory response syndrome. J Med Chem 2017;60(3):972–86. doi:10.1021/acs.jmedchem.6b01196.
[26] Food and Drug Administration. Guidance for industry, COVID-19: developing drugs and biological products for treatment or prevention. U.S. department of health and human services. Center for Drug Evaluation and Research (CDER). February 2021. Available from: https://www.fda.gov/media/137926/download [Last accessed February 15, 2024].
[27] WHO Working Group on the Clinical Characterisation and Management of COVID-19 InfectionA minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192–7. doi:10.1016/S1473-3099(20)30483-7.
[28] Schulz KF, Altman DG, Moher D, Group CONSORT. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332. doi:10.1136/bmj.c332.
[29] He S, Wang X. RIP kinases as modulators of inflammation and immunity. Nat Immunol 2018;19(9):912–22. doi:10.1038/s41590-018-0188-x.
[30] Silke J, Rickard JA, Gerlic M. The diverse role of RIP kinases in necroptosis and inflammation. Nat Immunol 2015;16(7):689–97. doi:10.1038/ni.3206.
[31] Clot PF, Farenc C, Suratt BT, Krahnke T, Tardat A, Florian P, Pomponio R, Patel N, Wiekowski M, Lin Y, Terrier B, Staudinger H. Immunomodulatory and clinical effects of receptor-interacting protein kinase 1 (RIPK1) inhibitor eclitasertib (SAR443122) in patients with severe COVID-19: a phase 1b, randomized, double-blinded, placebo-controlled study. Respir Res 2024;25(1):107. doi:10.1186/s12931-024-02670-z.