Auxora Versus Standard of Care for the Treatment of Severe or Critical COVID-19 Pneumonia: Results from a Randomized Controlled Trial

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Abstract

BACKGROUND

Calcium release-activated calcium (CRAC) channel inhibitors stabilize the pulmonary endothelium and block proinflammatory cytokine release, potentially mitigating respiratory complications observed in patients with COVID-19. This study aimed to investigate the safety and efficacy of Auxora, a novel, intravenously administered CRAC channel inhibitor, in adults with severe or critical COVID-19 pneumonia

METHODS

A randomized, controlled, open-label study of Auxora was conducted in adults with severe or critical COVID-19 pneumonia. Patients were randomized 2:1 to receive three doses of once-daily Auxora versus standard of care (SOC) alone. The primary objective was to assess safety and tolerability of Auxora. Additional outcomes included changes in clinical status based on an 8-point ordinal scale and the proportion of patients dying or requiring invasive mechanical ventilation in the 30 days after randomization.

RESULTS

In total, 17 patients with severe and three with critical COVID-19 pneumonia were randomized to Auxora and nine with severe and one with critical COVID-19 pneumonia to SOC. Similar proportions of patients receiving Auxora and SOC experienced ≥1 adverse event (75% versus 80%, respectively). Fewer patients receiving Auxora experienced serious adverse events versus SOC (30% versus 50%, respectively). Two patients (10%) receiving Auxora and two (20%) receiving SOC died in the 30 days after randomization. Among patients with severe COVID-19 pneumonia, median time to recovery with Auxora was five days versus 12 days with SOC; recovery rate ratio was 1.87 (95%CI, 0.72, 4.89). Invasive mechanical ventilation was needed in 18% of patients with severe COVID-19 pneumonia receiving Auxora versus 50% receiving SOC (absolute risk reduction=32%; 95%CI, -0.07, 0.71). One intubation or death over 30 days would be prevented by treating 2.6 patients with Auxora. Outcomes measured by an 8-point ordinal scale were significantly improved for patients receiving Auxora, especially for patients with a baseline PaO_2/FiO_2=101-200.

CONCLUSIONS

Auxora demonstrated a favorable safety profile in patients with severe or critical COVID-19 pneumonia and improved outcomes in patients with severe COVID-19 pneumonia. The impact of Auxora on respiratory complications in patients with severe COVID-19 pneumonia will be further assessed in a planned randomized, blinded, placebo-controlled study.

TRIAL REGISTRATION

ClinicalTrials.gov,NCT04345614. Retrospectively registered 14April2020 - https://clinicaltrials.gov/ct2/show/NCT04345614

Background

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease COVID-19, was first identified in December 2019 and designated a global pandemic by the World Health Organization in February 2020.[1] The majority of COVID-19 cases are mild, but up to 20% of patients develop severe or critical pneumonia, manifested by hypoxemia or respiratory failure necessitating mechanical ventilation, respectively.[1,2] COVID-19 pneumonia presents with a constellation of symptoms including fever, cough, and dyspnea, with infiltrates usually noted on lung imaging.[1,2] While the pathophysiology for COVID-19 pneumonia remains under investigation, there is an increasing body of literature to suggest a multifactorial lung injury and the important role of a hyperinflammatory state in its development.[3-5] Among patients with COVID-19 pneumonia, viral infiltration has been shown to cause severe endothelial injury and diffuse alveolar damage.[2-5] Furthermore, there appears to be an increase in proinflammatory cytokines leading to additional lung injury.[2-5] Together, these factors contribute to clinical deterioration, the need for invasive mechanical ventilation, and, in a substantial proportion of patients, death.[2-5]

Evidence suggests that calcium release-activated calcium (CRAC) channels play a role in inflammation-induced injury of pulmonary endothelial cells, resulting in loss of alveolar-capillary barrier function and extravasation of fluid into the alveoli.[6-9] CRAC channel activation is also linked to the production of proinflammatory cytokines associated with worsened outcomes in COVID-19.[7-11] Thus, inhibition of CRAC channels may be beneficial in preserving pulmonary endothelial integrity, reducing proinflammatory cytokine levels, and improving oxygenation in patients with COVID-19 pneumonia.[8,11-14]

CM4620 is a potent and selective CRAC channel inhibitor.[11-13,15] Preclinical work has demonstrated that in acute inflammatory conditions, CM4620 reduces inflammatory signals in the lung, protects tissues from calcium-induced damage and lowers serum and pulmonary proinflammatory cytokine levels.[7,9,11,12] Auxora, the novel intravenously administered nanoemulsion formulation of CM4620, rapidly distributes to the lungs and blocks CRAC channel dependent cytokine release within hours of its administration.[15] Based on these data and rationale, Auxora was investigated in patients with severe or critical COVID-19 pneumonia. The interim analyses presented here describe the safety of Auxora for all patients enrolled in the study; the efficacy analysis is limited to those with severe COVID-19 pneumonia.

Methods

Patient Selection

This Phase 2, randomized, controlled, open-label study was conducted across three centers in the United States (ClinicalTrials.gov number, NCT04345614). Patient enrolment took place from April 8, 2020 to May 13, 2020. Eligible patients were adults with a diagnosis of COVID-19 determined by reverse transcription polymerase chain reaction and pneumonia documented by chest imaging. In addition, patients were required to have ≥1 symptom consistent with COVID-19, such as fever, cough, sore throat, malaise, headache, muscle pain, dyspnea, confusion, or respiratory distress, and ≥1 clinical sign suggesting respiratory compromise, such as respiratory rate ≥30 breaths per minute, heart rate ≥125 bpm, SpO_2 <93% on room air or requiring >2L oxygen by nasal cannula to maintain SpO_2 ≥93%, or PaO_2/FiO_2 <300, imputed from pulse oximetry or determined by arterial blood gas.

Study Design

The initial study design included enrolment of 60 patients receiving low flow supplemental oxygen at screening into Arm A (severe COVID-19 pneumonia) and 60 patients receiving high flow supplemental oxygen through a high flow nasal cannula at screening into Arm B (critical COVID-19 pneumonia). In both arms, patients were randomly assigned in a 2:1 ratio to receive Auxora plus standard of care or standard of care alone. Auxora was administered on three consecutive days as a 4-hour continuous intravenous infusion. The initial dose was 2.0 mg/kg (max 250 mg) and subsequent doses were 1.6 mg/kg (max 200 mg) at 24 and 48 hours. All patients received local standard of care, including anti-viral agents, but investigational therapies and immunosuppressive medications were not permitted. At the discretion of the site investigators, patients treated with either Auxora or standard of care alone were able to receive convalescent plasma if they required invasive mechanical ventilation.

After admission, patients were assessed daily for the first ten days and then every 48 hours until Day 28 or discharge, whichever occurred first. On Day 30, all patients were assessed for mortality. Discharged patients were contacted by phone. All adverse events (AEs) and serious adverse events (SAEs) were recorded during hospitalization. The SpO_2 and FiO_2 at the time of the study visit and the lowest SpO_2/FiO2 ratio documented over the previous 24 hours were recorded daily. The patient's clinical status was also evaluated daily by assessing if the patient was alive, required invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), high flow supplemental oxygen or non-invasive ventilation, low flow supplemental oxygen, or other ongoing medical care in the previous 24 hours. The need for continued supplemental oxygen was also assessed at the time of discharge.

The trial protocol was approved by an institutional review board at each site and was overseen by an independent safety review committee (ISRC). Informed consent was obtained from either the patient or from the patient's legally authorized representative if the patient was unable to provide consent. The ISRC was scheduled to perform a review for each arm after the first 12 patients were dosed with Auxora and then again after 24 patients were dosed. The analysis plan called for a separate evaluation of the safety and efficacy of the two arms as enrolment rates were expected to differ. The ISRC conducted an initial review on May 3, 2020 after the first 12 patients in Arm A were dosed with Auxora. At that time, six patients had received standard of care in Arm A. The ISRC recommended continuing the trial without

changes. The US Food and Drug Administration (FDA) was sent the interim efficacy data presented here in response to questions about the ISRC review. The FDA provided guidance on May 12, 2020, to limit further enrolment in the open-label study and transition to a randomized, blinded, placebo-controlled study, and as such, both Arms A and B ceased further enrolment.

Statistical Analysis

All analyses were conducted in the Intention to Treat population. The primary objective was to determine the safety and tolerability of Auxora for patients with severe and critical COVID-19 pneumonia. The incidence, intensity, and relationship of AEs and SAEs, and the development of laboratory abnormalities that were clinically significant and required intervention were assessed. Mortality at Day 30 was evaluated as a safety outcome. For the purpose of safety and outcome analyses, patients from Arms A and B were analyzed together, comparing treatments with Auxora and standard of care with standard of care alone.

Efficacy outcome measures included recovery rate defined as the first day the patient satisfied criteria 6, 7, or 8 of the 8-point ordinal scale (Table 1). Additional efficacy outcome measures included the change in the 8-point ordinal scale over time, the proportion of patients requiring invasive mechanical ventilation, and a composite outcome of death or invasive mechanical ventilation. The number needed to treat (NNT) was calculated using the absolute risk reduction in the composite outcome in the Auxora group versus standard of care.

Efficacy analyses were performed in enrolled patients with severe COVID-19 pneumonia (Arm A) and in 3 subgroups of Arm A according to their baseline PaO_2/FiO_2 (1-100, 101-200, or ≥201). Baseline PaO_2/FiO_2 was defined as the lowest value in the 24 hours prior to screening. The PaO_2 was imputed from the SpO_2 using a published table based on Ellis's inversion of the Severinghaus equation.[16,17]

Results

Patients

At the time of cessation, 30 patients had been enrolled into the study. Of the 26 patients in Arm A, 17 were randomized to treatment with Auxora and nine to standard of care alone. Four patients were enrolled into Arm B: three to treatment with Auxora and one to standard of care alone (Figure 1). Across both arms, 18 patients (90%) received three doses of Auxora as assigned. One patient in Arm A received only one Auxora dose due to rapid improvement and early discharge. One patient in Arm B refused the third dose of Auxora. One patient in Arm B, who received all three doses, was transferred after 120 hours to another institution; their outcome was followed by the initial study team. In the standard of care group of Arm A, one patient withdrew from the study at 96 hours after being made Do Not Intubate (DNI) because of declining respiratory status. This patient was not included in the intubation analysis (Figure 1). All patients who did not die in the hospital completed the Day 30 assessment.

Baseline demographics were balanced across the Auxora and standard of care groups in Arm A (Table 2), but more patients in the Auxora group had diabetes (47%) than in the standard of care group (22%). The median time (min, max) from symptom onset to randomization was nine (4, 34) days in the Auxora group and seven (4, 11) days in the standard of care group. The baseline mean imputed PaO_2/FiO_2 was 178±74 in the Auxora group and 168±78 in the standard of care group. In Arm B, baseline characteristics were more variable due to the small sample size (Table 1). Individual patient listings for Arm A are presented in the supplementary appendix Figure S1.

Safety Outcomes

Across both arms, 15 patients (75%) receiving Auxora had ≥1 AE and six patients (30%) had ≥1 SAE. Site investigators judged three AEs, each occurring in three different patients, as being related to the administration of Auxora: an episode of itching, an increase in alkaline phosphate, and a rash. They were all were considered mild by the investigators and resolved. None of the reported SAEs were determined to be related to the administration of Auxora. Among patients receiving standard of care, eight (80%) had ≥1 AE and five (50%) had ≥1 SAE. There was no difference in AEs related to infections in the Auxora group when compared to standard of care (30% in each group).

Two patients (10%) treated with Auxora and two patients (20%) receiving standard of care died while hospitalized between ten and 17 days after randomization (supplementary appendix Figure S1). There were no deaths in the 30 days after randomization for patients who were discharged from the hospital. Both patients in the Auxora group and one patient in the standard of care group died while receiving invasive mechanical ventilation. The other patient receiving standard of care who died had been made DNI.

Efficacy Outcomes

Patients with severe COVID-19 pneumonia (Arm A) treated with Auxora had a shorter median time to recovery (five days) than patients treated with standard of care (12 days); the recovery rate ratio was 1.87 (95% confidence interval [CI], 0.72 to 4.89; Figure 2). In addition, three of 17 patients treated with Auxora (18%) were intubated compared to four of eight (50%) assigned to standard of care (95% CI, -0.07 to 0.71). The reduction was most pronounced in patients with a baseline PaO_2/FiO_2 between 101-200, in which only one of six patients (17%) treated with Auxora required intubation compared to three of four patients (75%) assigned to standard of care. A composite endpoint of death or invasive mechanical ventilation occurred less frequently in patients treated with Auxora (18%) compared to those assigned to standard of care (56%) with a hazard ratio of 0.23 (95% CI, 0.05 to 0.96; $P<0.05$; Figure 3). NNT was calculated as 2.6 patients needing to receive Auxora as opposed to standard of care for one patient to not have an outcome of death or invasive mechanical ventilation (Figure 4). No patients receiving Auxora or standard of care with a baseline PaO_2/FiO_2 >200 required invasive mechanical ventilation.

Clinical improvement, as measured by the mean of an 8-point ordinal scale, was greater in the Auxora group starting at Day 4, reaching statistical significance on Day 6, and remained significant from Day 9

through Day 12 (P<0.05; Figure 4). On Day 4, the odds ratio for clinical deterioration on the 8-point ordinal scale for the Auxora group compared to the standard of care group was 0.21 (95% CI, 0.04 to 0.098; P<0.05). The clinical improvement was most pronounced in patients with a baseline PaO_2/FiO_2 between 101-200, with the difference in means reaching statistical significance at Day 7; this was maintained through Day 12 (P<0.05; Figure 5).

Discussion

In this Phase 2, open-label, randomized, multicenter study of patients with severe or critical COVID-19 pneumonia, Auxora, a novel, intravenously administered CRAC channel inhibitor, demonstrated a potential therapeutic benefit in mitigating the respiratory complications of COVID-19. At the recommendation of the US FDA, this study was halted prior to completion of the originally planned 120 patients in order to transition to a randomized, placebo-controlled, double-bind study.

CRAC channel activation in the pulmonary endothelium is linked to the breakdown of the alveolar-capillary barrier.[7-9] CRAC channel activation also initiates the production and release of proinflammatory cytokines from immune cells.[10,11] The resulting development of pulmonary edema, hypoxemia, and ultimately ARDS contributes to the significant morbidity and mortality seen in COVID-19 pneumonia, particularly in those who eventually require invasive mechanical ventilation.[14,18] As demonstrated in animal models, inhibition of CRAC channels stabilizes pulmonary endothelial cells, blocks the release of proinflammatory cytokines and decreases vascular inflammation and permeability.[7,9,14] Given the direct effects on the pulmonary endothelium and the indirect effects on proinflammatory cytokine production, Auxora may be an attractive therapy for the management of patients with severe COVID-19 pneumonia.[7-9] Auxora has also demonstrated rapid distribution to the lungs, resulting in a fast onset of action that is reversible in 24 to 48 hours (unpublished observations).

The data available at the time of study termination indicate an encouraging safety profile for Auxora, with no increase in the proportion of patients experiencing AEs or SAEs when compared with standard of care. Furthermore, patients receiving Auxora had a more favorable clinical course than patients receiving standard of care as reflected by the rapid time to recovery, the decreased need for invasive mechanical ventilation, and greater improvement in clinical outcomes as documented by the difference in 8-point ordinal scale. Analysis of the ordinal scale over time also suggested greater odds of improvement in patients treated with Auxora beginning on Day four, with the most pronounced clinical benefit in patients with a PaO_2/FiO_2 ratio between 101-200.

The ideal timing and duration of intervention in the course of COVID-19 pneumonia remains unknown.[19] There are some concerns that premature immunomodulation may inhibit host anti-viral immunity and delay viral clearance, while delaying immunomodulation may prove futile if acute pulmonary injury is advanced. The PaO_2/FiO_2 ratio, imputed from the SpO_2/FiO_2, could serve as a simple means of determining both the optimal timing of intervention and the patients most likely to benefit[16,17]; it should

be incorporated into other studies of therapies for COVID-19. Currently, patients are only being categorized by the receipt of either low flow supplemental oxygen or high flow supplemental oxygen, but this approach may not capture the severity of lung injury, may mask patients who are likely to respond to treatment and is limited by substantial inter-institution variations in practice.

Our findings, and those from recent remdesivir and RECOVERY trials, raise consideration for a two-pronged approach for the treatment of COVID-19 pneumonia.[19,20] Preliminary results of remdesivir for the treatment of COVID-19 demonstrated reduced time to recovery, but treatment alone with an antiviral therapy is unlikely to be sufficient in improving outcomes.[19] It may be possible, however, to improve patient outcomes by combining an antiviral treatment with immunomodulation to address the inflammatory response. Preliminary results from the RECOVERY trial demonstrated that after 10 days of receiving dexamethasone once-daily, the 28-day mortality rate was reduced by 35% in patients with COVID-19 requiring ventilation and by 20% in patients receiving only oxygen.[20] The 28-day mortality rate in patients receiving only oxygen assigned to standard of care was 25%. The 28-day mortality rates in the RECOVERY trial for patients receiving low flow supplemental oxygen versus high flow supplemental oxygen, and the proportion of patients who progressed to mechanical ventilation were unannounced in the press release.[20] As Auxora is associated with a rapid onset of action and a rapid cessation of action, it works quickly to reduce proinflammatory cytokines while preserving pulmonary endothelial integrity, without excessive immunosuppression.[15] Coupled with the low 28-day mortality rate (10%) presented here, Auxora may allow for improved patient outcomes when used in combination with dexamethasone. Additional clinical trials are needed to understand the effect of these combinations of therapy.

The interpretation of the results of this study is limited by the open-label design and small sample size. Additionally, the significant imbalances in age and medical comorbidities between the three patients receiving Auxora and one patient receiving standard of care in Arm B prevented a meaningful direct comparison between the two groups with critical COVID-19 pneumonia. It was observed that the proportion of patients treated with Auxora who had diabetes, a co-morbidity associated with poorer outcome in COVID-19, was double that for patients receiving standard of care alone. Manufacturing and administration of a placebo was sacrificed given the need to initiate the study rapidly during the global pandemic with associated constraints on healthcare resources. These constraints, including adequate personal protective equipment, also limited the ability of research teams to obtain research-specific cytokine levels, which if obtained, may have further supported the mechanisms of Auxora.

Conclusions

The favorable safety profile and the strong efficacy signals in the interim analysis of this Phase 2 study support the need for further investigation of the novel CRAC channel inhibitor, Auxora, in patients with severe COVID-19 pneumonia. In addition, the results suggest the potential for the clinical development of Auxora for the treatment of other etiologies of acute respiratory distress syndrome. A randomized, placebo-controlled, double-blind study will soon be underway to test the efficacy of Auxora in

combination with local standard of care, likely remdesivir and/or dexamethasone, for the management of patients with severe COVID-19 pneumonia.

Abbreviations

AEs, adverse events

CRAC, calcium release-activated calcium channels

DNI. Do not intubate

ECMO, extracorporeal membrane oxygenation

FDA, Food and Drug Administration

ISRC, independent safety review committee

NNT, number needed to treat

SAEs, serious adverse events

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Declarations

Ethics approval and consent to participate

The trial protocol was approved by an institutional review board at each site and was overseen by an ISRC. The trial was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the local institutional review boards. Informed consent was obtained from either the patient or from the patient's legally authorized representative if the patient was unable to provide consent. This trial is registered at ClinicalTrials.gov number, NCT04345614.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the Clinical Study Report being finalized but will be available from the corresponding author on reasonable request at a later time

Competing interests

JM reports grants from CalciMedica, Inc. during the conduct of the study; and grants from CalciMedica, Inc. and Abbott Labs outside of the present work. JZ reports personal fees from CalciMedica, Inc. related to the present work. KS and SH are employees of, and hold stock in, CalciMedica, Inc. CB, MS, SA, AL, ZS declare no competing interests.

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Authors' contributions

JM, CB, JZ, KS, and SH were involved in the study design and protocol development. All authors were involved in this clinical trial. JM and CB contributed equally to this article. JZ conducted the statistical analysis. All authors reviewed, revised, and approved the final version of the manuscript.

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Tables

Table 1. 8-Point Ordinal Scale.

Scale	Description
1	Death
2	Hospitalized, requiring invasive mechanical ventilation or ECMO
3	Hospitalized, requiring noninvasive mechanical ventilation or high flow supplemental oxygen
4	Hospitalized, requiring low flow supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
6	Hospitalized, not requiring supplemental oxygen or ongoing medical care
7	Discharged, requiring supplemental oxygen
8	Discharged, not requiring supplemental oxygen

Efficacy outcome measured with the 8-point ordinal scale included recovery rate defined as the first day the patient satisfied criteria 6, 7, or 8 and change in the 8-point ordinal scale over time. ECMO, Extracorporeal membrane oxygenation

Table 2. Baseline demographics and clinical characteristics.

	Arm A*		Arm B†	
	Auxora (n=17)	SOC (n=9)	Auxora (n=3)	SOC (n=1)
Age, years (mean±SD)	59±12	61±13	64±14	36±NA
Median BMI, kg/m^2 (min, max)	30 (25, 79)	30 (23, 49)	23 (18, 36)	34
Male sex, n (%)	7 (41)	5 (56)	1 (33)	1 (100)
Ethnicity, n (%)				
White	8 (47)	5 (56)	1 (33)	0
Black or African American	7 (41)	3 (33)	1 (33)	1 (100)
Asian	0	1 (11)	1 (33)	0
Other/Multiple	2 (12)	0	0	0
Hispanic or Latino, n (%)	2 (12)	1 (11)	0	0
Diabetes, n (%)	8 (47)	2 (22)	2 (67)	0 (0)
Hypertension, n (%)	8 (47)	4 (44)	2 (67)	0 (0)
Median time from onset of symptoms to randomization, days (min, max)	9 (4, 34)	7 (4, 11)	11 (8, 17)	13
Ferritin, ng/mL (mean±SD)	709±553	772±742	1776±722	2151±NA
CRP, mg/dL (mean±SD)	10±7	12±6	14±11	9±NA
PaO_2/FiO_2 (mean±SD)	178±74	168±78	106±45	87±NA
PaO_2/FiO_2 ≥201	7 (41)	3 (33)	0	0
PaO_2/FiO_2 101-200	6 (35)	4 (44)	2 (67)	0
PaO_2/FiO_2 ≤100	4 (24)	2 (22)	1 (33)	1 (100)
PaO_2/FiO_2 101-200 Ferritin ng/mL (mean±SD)	867±712	910±1090	1637±963	NA
PaO_2/FiO_2 101-200 CRP mg/dL (mean±SD)	11±5	13±9	16±15	NA

Baseline demographics were balanced across the Auxora and standard of care groups in Arm A. In Arm B, baseline characteristics were more variable due to the small sample size. *Patients in Arm A included those who were receiving low flow supplemental oxygen at screening and were defined by regulatory guidance as having severe COVID-19 pneumonia; †Patients in Arm B included those who were receiving high flow supplemental oxygen through a high flow nasal cannula at screening and were defined by regulatory guidelines as having critical COVID-19 pneumonia. NA, not available; SOC, standard of care.

Figures

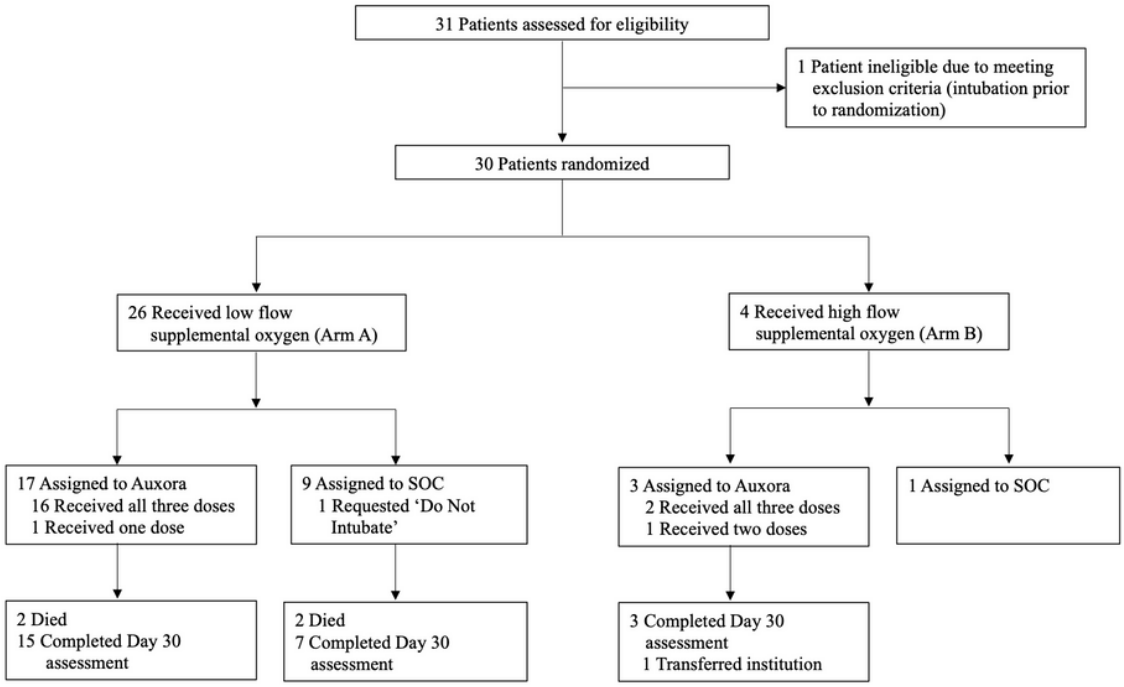

Figure 1

Patient Enrolment and Randomization. One patient in Arm A received only 1 Auxora dose due to rapid improvement and early discharge and 1 patient in Arm B refused the third dose of Auxora. One patient in Arm B, who received all 3 doses, was transferred after 120 hours to another institution. In the standard of care group of Arm A, 1 patient withdrew from the study at 96 hours after being made Do Not Intubate (DNI) because of declining respiratory status.

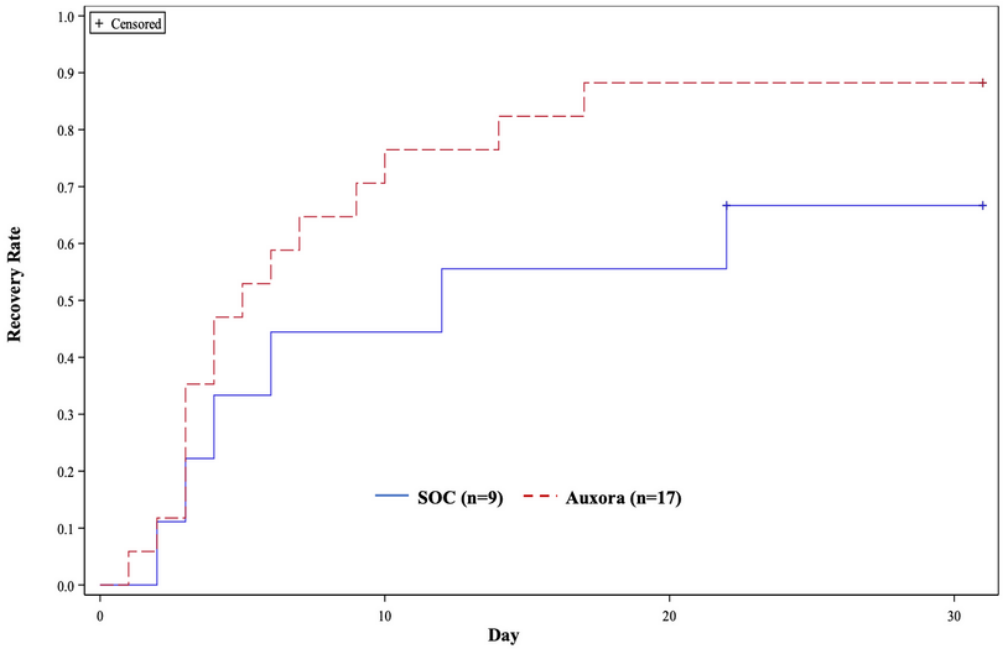

Figure 2

Recovery Rate Among Patients with Severe COVID-19 Pneumonia. Recovery rate defined as the first day the patient satisfied criteria 6, 7, or 8 of the 8-point ordinal scale. Patients receiving Auxora had a shorter median time to recovery (5 days) than patients treated with standard of care (12 days); recovery rate ratio was 1.87 (95% CI, 0.72 to 4.89). Patients with severe COVID-19 pneumonia were receiving low flow supplemental oxygen (Arm A).

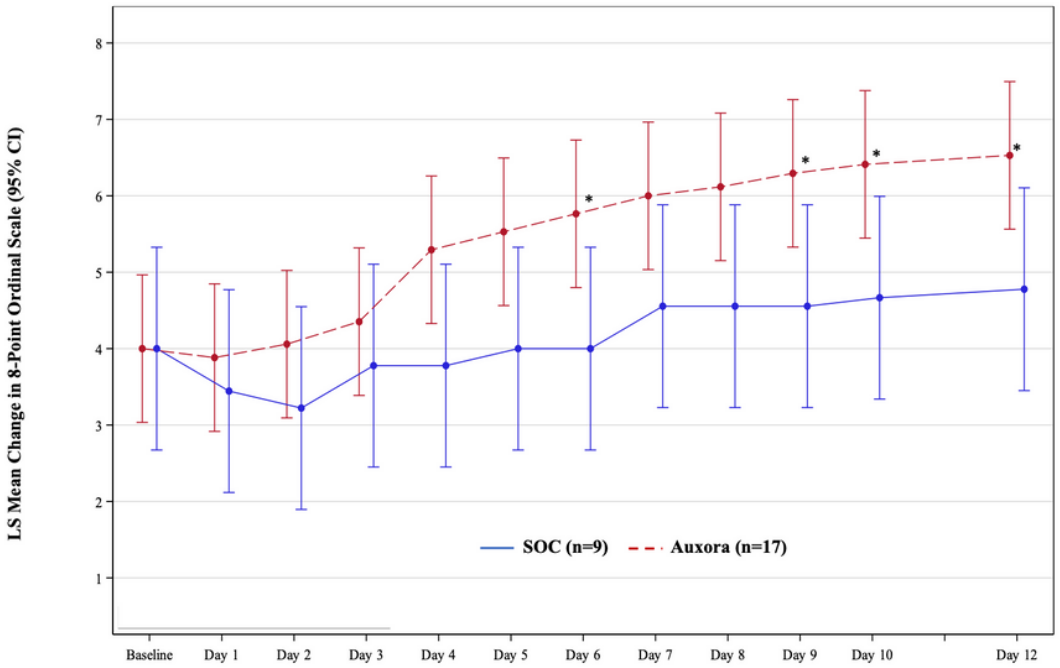

Figure 3

Change in 8-Point Ordinal Scale Over Time in Patients with Severe COVID-19 Pneumonia. Mean difference was statistically significant for Auxora (n=17) when compared with standard of care (n=9) at Day 6 and Days 9 through 12 (*P<0.05 versus standard of care). Patients with severe COVID-19 pneumonia were receiving low flow supplemental oxygen (Arm A).

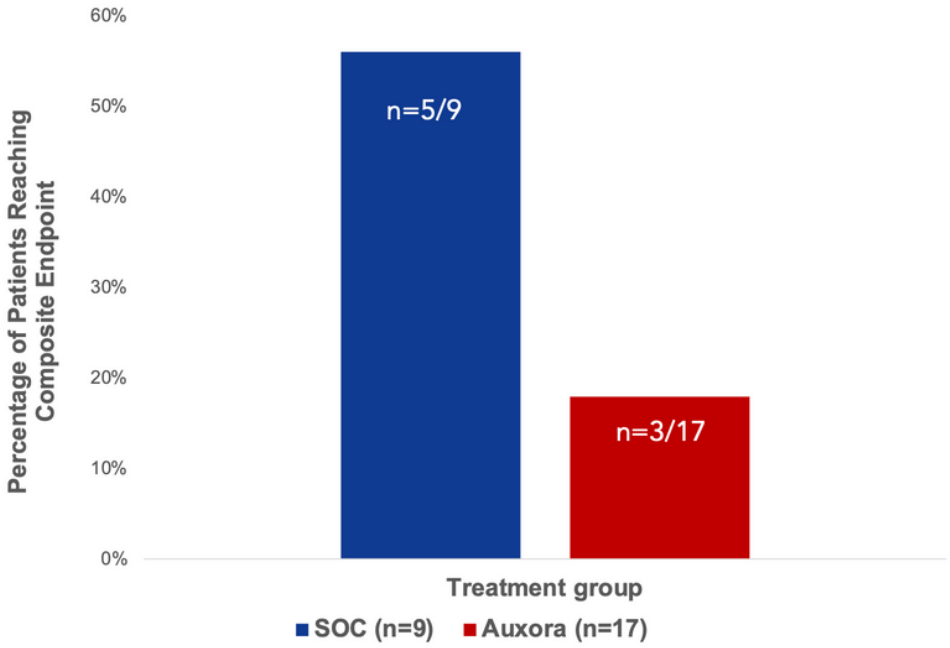

Figure 4

Percentage of Patients with Severe COVID-19 Pneumonia Reaching Composite Endpoint. The composite endpoint was defined as needing invasive mechanical ventilation or death in the 30 days after randomization. The NNT was calculated as 2.6 patients needing to receive Auxora as opposed to standard of care for one patient to not have an outcome of death or invasive mechanical ventilation. Hazard ratio was 0.23 (95% CI, 0.05 to 0.96; P<0.05). Patients with severe COVID-19 pneumonia were receiving low flow supplemental oxygen (Arm A).

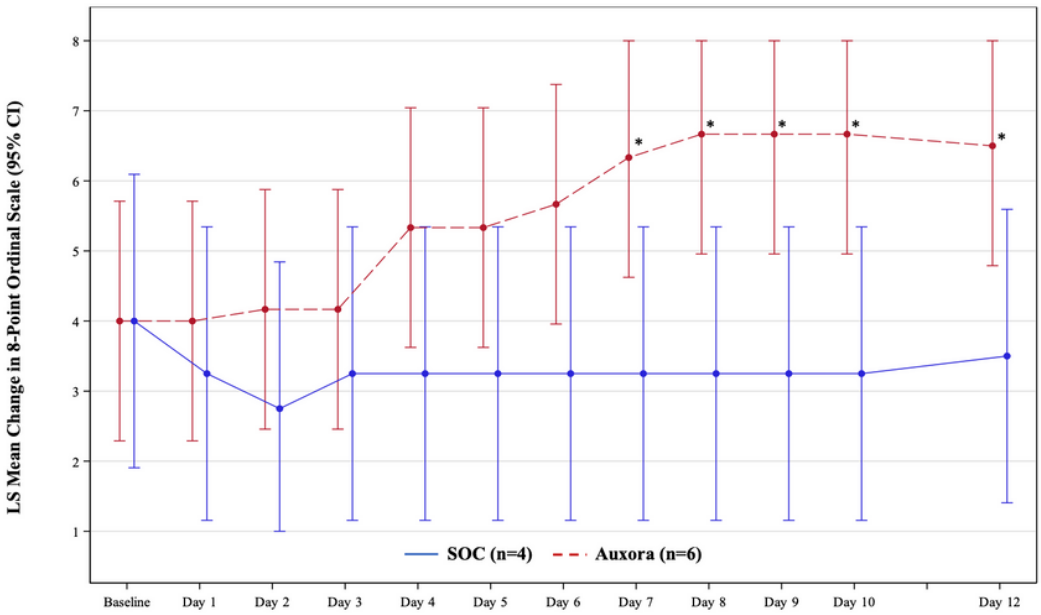

Figure 5

Change in 8-Point Ordinal Scale in Patients with Severe COVID-19 Pneumonia with PaO2/FiO2 Between 101-200. Mean difference was statistically significant from Day 7 through Day 12 for patients receiving Auxora (n=6) compared with those receiving standard of care (n=4 ; *P<0.05 versus standard of care). Patients with severe COVID-19 pneumonia were receiving low flow supplemental oxygen (Arm A).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryAppendixAuxoraManuscript21Jun2020.docx