# Auxora Vs. Placebo for the Treatment of Patients with Severe COVID-19 Pneumonia: A Randomized Clinical Trial

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# Abstract

**Background:** Calcium release-activated calcium (CRAC) channel inhibitors block proinflammatory cytokine release, preserve endothelial integrity and may effectively treat patients with severe COVID-19 pneumonia.

**Methods:** CARDEA was a phase 2, randomized, double-blind, placebo-controlled trial evaluating the addition of Auxora, a CRAC channel inhibitor, to corticosteroids and standard of care in adults with severe COVID-19 pneumonia. The primary endpoint was time to recovery through Day 60, with secondary endpoints of all-cause mortality at Day 60 and Day 30. Due to declining rates of COVID-19 hospitalizations and encroachment of prohibited medications as standard of care, the trial was stopped early.

**Results:** The pre-specified efficacy set consisted of the 261 patients with a baseline imputed $PaO_2/FiO_2$ £200 with 130 and 131 in the Auxora and placebo groups, respectively. Time to recovery was 7 vs. 10 days (*P*=0.0979) for patients who received Auxora vs. placebo, respectively. The all-cause mortality rate at Day 60 was 13.8% with Auxora vs. 20.6% with placebo (*P*=0.1449); Day 30 all-cause mortality was 7.7% and 17.6%, respectively (*P*=0.0165). Similar trends were noted in patients on high flow nasal cannula at baseline or those with a baseline imputed $PaO_2/FiO_2$ ≤100. Serious adverse events occurred less frequently in patients treated with Auxora vs. placebo.

**Conclusions:** Auxora was safe and well tolerated with strong signals in both time to recovery and all-cause mortality through Day 60 in patients with severe COVID-19 pneumonia. Further studies of Auxora in combination with corticosteroids and other immunomodulatory agents are warranted.

**Trial registration:** NCT04345614


# Introduction

The COVID-19 pandemic has caused nearly 5.5 million deaths worldwide and more than 820,000 deaths in the US.[1] Although most cases are asymptomatic or mild, up to 20% of patients progress to develop severe pneumonia, requiring hospitalization and intensive care, with mortality rates near 30% in high-risk groups.[2-6] In the US alone, more than 2.6 million patients with COVID-19 have been hospitalized.[7] To address this global health crisis, antiviral treatments have been utilized to decrease the time to recovery and immunomodulatory therapies have been administered as they have demonstrated some efficacy at reducing mortality among hospitalized patients but additional novel therapeutics are urgently needed.[8-10]

The pathophysiological course of COVID-19 pneumonia proceeds in two distinct phases; an initial viral replication followed by an excessive, dysregulated host immune response leading to alveolitis and hypoxemic respiratory failure.[3,6,11-14] Autopsy examinations of COVID-19 infected lungs have revealed intense inflammasome formation, diffuse alveolar damage, and microvascular thrombosis.[6,15] Recent evidence suggests that alveolitis observed in these patients results from the positive feedback loop

between monocyte-derived alveolar macrophages and T cells.[16] Tissue resident alveolar macrophages respond to SARS-CoV-2 infection in the lung by producing T-cell chemoattractants. Arriving T cells produce interferon-gamma (IFNg), leading to further alveolar macrophage activation and recruitment of monocyte-derived alveolar macrophages.[15,16] The feedback loop leads to a rapid increase in proinflammatory cytokines, diffuse alveolar injury, severe endothelialitis, and eventual acute respiratory distress syndrome (ARDS) leading to multiorgan dysfunction and failure.[14,17,18] These pathophysiologic events suggest that treatments with broad-based immunomodulatory effects may be more effective than those targeting specific immune pathways.[19] One such potential treatment is Auxora, a calcium release-activated calcium (CRAC) channel inhibitor that lowered mortality in an open-label trial of patients with severe COVID-19 pneumonia.[20]

CRAC channels have been shown to play important roles in several cell types and pathways linked to COVID-19 pneumonia.[21] These channels are mainly composed of the plasma membrane $Ca^{2+}$ conductance protein Orai1 and the endoplasmic reticulum (ER) $Ca^{2+}$ sensing protein stromal interaction molecule 1 (STIM1).[21] When $Ca^{2+}$ is released from the ER, the drop in ER luminal $Ca^{2+}$ concentration is sensed by STIM1, which undergoes a conformational change resulting in Orai1 activation and $Ca^{2+}$ entry into the cell.[21] Blockade of CRAC channels with the selective Orai1 CRAC channel inhibitor Auxora abrogates the release of multiple proinflammatory cytokines from human lymphocytes, including interleukin (IL)-6, IL-17, and IFNg that are implicated in COVID-19 alveolitis (Figure 1).[16,22] Since the $Ca^{2+}$ entering through CRAC channels in T cells primarily activates the calcineurin/nuclear factor of activated T-cells signal transduction pathway, CRAC channel inhibitors may act cooperatively with anti-inflammatory drugs such as dexamethasone that work through the NF-kB signal transduction pathway.[23-25]

Pathophysiologically-activated CRAC channels have also been associated with pulmonary endothelial cell dysfunction and plasma extravasation in animal models of acute lung injury.[26] CRAC channel inhibition in these models protects endothelial cells and reduces inflammation and plasma extravasation.[27,28] Finally, although the role of CRAC channels in monocyte functioning is still emerging, release of reactive oxygen species from monocytes has been shown to be controlled by Orai1 CRAC channels.[29] Thus, inhibition of CRAC channels by Auxora may provide the kind of broad-based approach likely to be effective in treating patients with severe COVID-19 pneumonia (Figure 1).[16]

# Methods

*Trial Design and Oversight*

CARDEA was a phase 2, randomized, double blind, placebo-controlled trial that tested the addition of Auxora to corticosteroids and standard of care in patients with severe COVID-19 pneumonia (ClinicalTrials.gov identifier, NCT04345614). Patients were randomized 1:1 to Auxora plus standard of care or placebo plus standard of care. Randomization was stratified by baseline imputed $PaO_2/FiO_2$ ratio

of >200 vs ≤200 through a central, concealed, web-based, automated system. An independent statistician created the randomization schedule with stratified block randomization method using SAS proc plan procedure. Within each stratum, the treatment codes were assigned at a 1:1 ratio of Auxora and placebo with the block size of 4. The $PaO_2/FiO_2$ was imputed using a non-linear equation from a $SpO_2/FiO_2$ ratio obtained using pulse oximetry. The baseline $PaO_2/FiO_2$ was the worst value in the 24 hours prior to screening.

Auxora was administered by a 4-hour IV infusion at 2.0 mg/kg (1.25 mL/kg) at 0-hour and 1.6 mg/kg (1 mL/kg) at 24 and 48 hours. Placebo was dosed at 1.25 mL/kg at 0-hour and 1 mL/kg at 24 and 48 hours. Patients were assessed immediately before each infusion. Seventy-two hours after the start of the first infusion, patient assessment occurred every 24 hours (±4 hours) until 240 hours and then continued every 48 hours until Day 30 or discharge. The ordinal scale was assessed daily for patients in a standardized manner as described in the electronic case report form. Patients discharged before Day 25 were contacted at Day 30 (±5 days). All patients were contacted for a follow-up safety and mortality assessment at Day 60 (±5 days). Public information (e.g., death reports, governmental information) was used by sites to ascertain Day 60 mortality status in patients who refused direct contact or had withdrawn from the trial. All patients were required to receive dexamethasone or equivalent dose of another corticosteroid as well as pharmacological prophylaxis against development of venous thromboembolic disease. Remdesivir use was recommended for all patients, and convalescent plasma administration was allowed according to local standard of care. Other immunomodulators for the treatment of COVID-19 pneumonia, including tocilizumab and JAK inhibitors, were prohibited due to regulatory guidance.

An institutional review board at each site approved the trial protocol. Informed consent was obtained from the patient or the patient's legally authorized representative if the patient was unable to provide consent. The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and was sponsored by CalciMedica, Inc (La Jolla, CA). An independent data monitoring committee (IDMC) provided trial oversight. Operational support was provided by Bionical-Emas (Paulsboro, NJ) and Princeton Pharmatech (San Francisco, CA) performed the statistical analyses. All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial adherence to the protocol.

The IDMC first reviewed unblinded safety data once 57 patients were randomized, then again after 70 patients with a baseline imputed $PaO_2/FiO_2$ ≤200 completed 60 days of the trial, and finally after randomization of 209 patients with a baseline imputed $PaO_2/FiO_2$ ≤200. The IDMC also performed an interim sample size re-estimation based on the recovery rate ratio after 70 patients with a baseline imputed $PaO_2/FiO_2$ ≤200 reached Day 60.

The trial was initially designed to enroll up to 400 patients, with a maximum of 80 patients having a baseline imputed $PaO_2/FiO_2$ >200. The Sponsor capped the number of patients with a baseline imputed $PaO_2/FiO_2$ >200 at the time of the first IDMC review because a blinded analysis showed that no

patients in this subgroup required mechanical ventilation or died during hospitalization. Due to declining rates of US COVID-19 hospitalizations in the spring of 2021, and the more frequent use of tocilizumab in CARDEA candidate patients at many trial sites following recommendations by the National Institutes of Health's COVID-19 Treatment Guidelines Panel,[30] the Sponsor elected to stop the trial early following discussions at the third IDMC review.

*Patient Population*

Eligible patients were adults with a laboratory-confirmed diagnosis of COVID-19 determined by polymerase chain reaction or other assay and pneumonia as documented by chest imaging. Patients were required to have ≥1 symptom consistent with COVID-19 and respiratory failure, defined as baseline imputed $PaO_2/FiO_2$ ≤300, requiring oxygen therapy using either a high flow (HFNC) or low flow nasal cannula. Patients with a baseline imputed $PaO_2/FiO_2$ ≤75 and those receiving either non-invasive mechanical ventilation or invasive mechanical ventilation and current treatment with immunosuppressive medications or immunotherapy were excluded from the trial. Full entry criteria are available in the Supplementary Appendix.

*Outcomes*

The primary endpoint was time to recovery through Day 60, defined as meeting the criteria for category 6 (Hospitalized, not requiring supplemental oxygen or ongoing medical care), category 7 (Discharged, requiring supplemental oxygen), or category 8 (Discharged, not requiring supplemental oxygen) using an 8-point ordinal scale. The key secondary endpoint of all-cause mortality at Day 60 was requested by regulatory guidance. Additional secondary endpoints evaluated in the efficacy set included all-cause mortality at Day 30, the proportion of patients requiring invasive mechanical ventilation or death through Day 60, the proportion of patients requiring invasive mechanical ventilation through Day 60, and differences in outcomes measured by the 8-point ordinal scale through Day 60. Safety endpoints included the occurrence and severity of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs).

The primary and key secondary endpoints were also evaluated in pre-specified subgroups of patients who required oxygen therapy via either HFNC or low flow nasal cannula at baseline or patients having an imputed $PaO_2/FiO_2$ ≤100 or 101-200 at baseline, and in all randomized patients. The safety endpoints were evaluated in all patients who received study drug, including those with an imputed $PaO_2/FiO_2$ >200.

*Statistical Analysis*

The efficacy set was pre-specified, consisting of those patients with a baseline imputed $PaO_2/FiO_2$ ≤200. A two-group log-rank test with a 0.05 two-sided significance level would have 90% power to detect a difference in the recovery rate ratio of approximately 1.49 in the 320 patients with a baseline imputed PaO2/FiO2 ≤200 who were randomized 1:1 to Auxora or placebo. The Sponsor elected to not change the sample size after the IDMC performed the sample size re-estimation.

Time to recovery through Day 60 was compared between the Auxora and placebo groups using log-rank test stratified by baseline imputed $PaO_2/FiO_2$ ≤100 vs. 101-200 and displayed using a Kaplan-Meier estimate. Patients were censored at the last ordinal scale assessment if no recovery event was observed during the study.

All-cause mortality at Day 60 was compared between the Auxora and placebo groups using a Cochran-Mantel- Haenszel test stratified by the baseline imputed $PaO_2/FiO_2$ ≤100 vs. 101-200. In addition, a sensitivity analysis was performed that estimated the 60-day death rate with hypothesis testing based on the Kaplan-Meier estimates and standard errors estimated by Greenwood formula using the log-log transformation of the survival function stratified by the baseline imputed $PaO_2/FiO_2$ of ≤100 vs. 101-200.

To protect the trial level type 1 error rate at α=5% (two sided) between the primary endpoint analysis and the key secondary endpoint analysis, the Benjamini and Hochberg testing strategy was used as test statistics of time to recovery and all-cause mortality at Day 60 were positively correlated.

### Role of funding source

The funder of the study had primary responsibility for the study design, protocol development, study monitoring, data management and interpretation, and statistical analyses. The funder also contributed to the drafting of the manuscript and decision to submit.

## Results

*Patients*

Patient enrollment occurred from September 8, 2020 to May 24, 2021. A total of 284 patients were randomized across 17 US centers, 143 to Auxora and 141 to placebo (Figure 2), and 281 patients received at least one dose of study drug. The efficacy set consisted of 261 patients with a baseline imputed $PaO_2/FiO_2$ ≤200 with 130 in Auxora and 131 in placebo groups (Figure 2). All patients (100%) in the efficacy set received corticosteroids (85.8%, dexamethasone), 75.9% received remdesivir, and 99.6% received anticoagulation (93.1%, enoxaparin [dosed for venous thromboembolic disease prophylaxis]; Table S1). Tocilizumab, while a prohibited medication, was administered to 8 patients after randomization, and 6 were determined to have received placebo after unblinding.

Baseline characteristics were well balanced between the Auxora and placebo groups in the efficacy set (Table 1) and among all randomized patients (Table S2). The median age was 60 years; 67.4% were male, and 39.5% were Hispanic or Latino. The median time from symptom onset to randomization was 12 days, and 62.5% required oxygen therapy via HFNC at baseline; 44.8% of patients had an imputed $PaO_2/FiO_2$ ≤100 at baseline.

*Time to Recovery*

Recovery through Day 60 occurred in 79.2% and 74% of patients in the Auxora and placebo groups, respectively (Table 2). The median time to recovery was 7 days (95% CI, 6.0, 9.0) and 10 days (95% CI, 7.0, 14.0; *P*=0.0979) for patients in the Auxora and placebo groups, respectively. In the subgroups of patients who required oxygen therapy via HFNC at baseline or had an imputed $PaO_2/FiO_2$ ≤100 at baseline, a higher percentage of patients in the Auxora group recovered and patients in the Auxora group had a faster time to recovery, compared to the placebo group (Table 3). Similar results were noted when all randomized patients were analyzed (Table S3).

*All-Cause Mortality*

The all-cause mortality rate at Day 60 was 13.8% (n=18) in patients treated with Auxora and 20.6% (n=27) with placebo (difference -6.75; 95% CI -15.75, 2.24; *P*=0.1449; Table 2; Figure S1). The all-cause mortality rate at Day 30 was 7.7% in patients treated with Auxora and 17.6% with placebo (difference -9.86; 95% CI -17.80, -1.83; *P*=0.0165; Table 2; Figure S1). Lower mortality rates at Day 60 were observed in subgroups of patients using HFNC at baseline or those with an imputed $PaO_2/FiO_2$ ≤100 at baseline (Table 3; Figures S2, S3) and in all randomized patients (Table S3). Additional pre-specified subgroup analyses for mortality are noted in Figure S4.

Additional secondary endpoints demonstrated potential benefits with Auxora vs. placebo (Table 2), including a higher proportion of patients receiving Auxora being discharged, and a lower proportion progressing to invasive mechanical ventilation, extracorporeal membrane oxygenation, and death at Day 60 (Odds Ratio, 0.647; 95% CI 0.405, 1.031; *P*=0.0672) and Day 30 (Odds Ratio, 0.617; 95% CI 0.387, 0.983; *P*=0.0423; Figure 3).

*Safety Outcomes*

In total, 34 patients (24.1%) in the Auxora and 49 (35.0%) in the placebo groups experienced SAEs. The most common were respiratory failure, ARDS, and pneumonia (Table 4). Discontinuation due to TEAEs occurred in 3 patients in the Auxora and 5 patients in the placebo groups. The most common TEAEs were respiratory failure, increasing triglycerides, hyperglycemia, and acute kidney injury. No cases of increased triglycerides were classified as serious.

# Discussion

Consistent with previously published data, results from this trial indicate a potential therapeutic benefit of Auxora in addition to corticosteroids and standard of care in patients with severe COVID-19 pneumonia.[20] While not statistically significant, more patients with a baseline imputed $PaO_2/FiO_2$ ≤200 who received Auxora met the primary endpoint of recovery through day 60 and in fewer days than those who received placebo. Patients who received Auxora had a lower all-cause mortality rate at both Days 60 and 30, the latter being statistically significant. Patients, who required oxygen therapy via HFNC at baseline or had an

imputed $PaO_2/FiO_2$ ≤100 at baseline may have benefited the most from the addition of Auxora to corticosteroids and standard of care.

Notable in the trial design was the imputation of the $PaO_2/FiO_2$ based on measured oxygen saturation using pulse oximetry. Imputation of the $PaO_2/FiO_2$ was validated in mechanically ventilated patients enrolled in the NHLBI ARDS Network and PETAL Network and facilitated enrollment of 94 patients in the NHLBI PETAL Network ROSE trial.[31-33] In many COVID-ARDS trials, eligibility criteria for hypoxemia are incorporated into their study design; however, we are aware of only one other trial studying severe or critical COVID-19 pneumonia that allowed $PaO_2/FiO_2$ imputation as an entry criterion.[34] This study, and the previous open-label study,[20] suggests that patients with an imputed $PaO_2/FiO_2$ >200 respond well to corticosteroids alone and may not need additional immunomodulatory therapy to avert mortality, while those with a level ≤200 remain at a high risk for mortality and need further immunomodulation.

Limitations in this study include the premature capping of patients with an imputed $PaO_2/FiO_2$ >200 and the early termination of the study. The decision to limit the number of patients with an imputed $PaO_2/FiO_2$ >200 was made following a blinded analysis that showed this patient population was not at increased risk for mortality or mechanical ventilation with current standard of care and did not require additional immunomodulatory therapies beyond corticosteroids. Further, the early termination was in part due to tocilizumab, a medication prohibited by regulatory guidance during trial design, being routinely administered, and that by May of 2021, US COVID-19 hospitalizations had significantly declined, reducing the number of patients that met inclusion criteria. While this study should be considered as proof-of-concept for the use of Auxora in the treatment of patients with severe COVID-19 pneumonia, the potential benefit of Auxora will need to be re-assessed in combination with both corticosteroids and other immunomodulatory agents.

# Conclusions

Mechanistically, CRAC-channel inhibitors, such as Auxora, may have therapeutic efficacy in both hastening recovery and reducing mortality in severe COVID-19 pneumonia, and as such, warrant continued clinical development. Results from this phase 2 trial demonstrated that Auxora was safe and well tolerated with strong signals in both time to recovery and all-cause mortality. This trial's results provide support for a phase 3 trial of Auxora in patients with severe COVID-19 pneumonia and receiving both corticosteroids and other immunomodulatory agents.

# Abbreviations

AEs, adverse events

ARDS, acute respiratory distress syndrome

CRAC, calcium release-activated calcium channels

ECMO, extracorporeal membrane oxygenation

ER, endoplasmic reticulum

HFNC, high flow nasal cannula

IDMC, independent data monitoring committee

IFNg, interferon-gamma

IL, interleukin

NHLBI, National Heart, Lung, and Blood Institute

SAEs, serious adverse events

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

STIM1, stromal interaction molecule 1

TEAEs, treatment-emergent adverse events

US, United States

# 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 IDMC. The trial was conducted in accordance with Good Clinical Practice guidelines and 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 upon request.

### Competing interests

KS and SH are full time employees of CalciMedica and hold stock options. CB and RMA report consulting fees not related to this manuscript with CalciMedica. JM reports grants to institution from CalciMedica. PCH reports grant/contract payments made to his institution from CalciMedica, National Institute of Health, US Department of Defense, US Center for Disease Control, Good Ventures, Rapid Pathogen Screening, Novartis, Kinevant Sciences GmbH, Mesoblast, Ophirex, Inc., Faron Pharmaceuticals, Day Zero Diagnostics, and iDoc Telehealth Solutions. JZ reports payment and consultant fees to Princeton Pharmatech. MA, MT, and EM report no conflicts of interest.

### Funding

This study was funded by CalciMedica, Inc. (La Jolla, CA, USA). The study was designed by the funder (CalciMedica, Inc., La Jolla, CA, USA) with input from the lead investigators (CB, MA, PCH). The funder compiled and analyzed the study data and interpreted data in collaboration with all authors. All authors had full access to all the data in the study and provided input on the analyses before and during writing of the report and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author wrote the first draft of the report and the funder commissioned medical writing assistance from Sarah Odeh (San Francisco, CA, USA) to support subsequent drafts under the direction of all authors. All authors reviewed and revised each draft and approved the final submitted version. The corresponding author had final responsibility for the decision to submit for publication.

### Authors' contributions

CB, MA, JZ, KS, SH, and PCH contributed to the trial concept and design, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the trial or data collection. JZ, KS, and SH verified the data and reviewed the statistical analysis. CB, MA, JZ, KS, SH, and PCH interpreted the data, drafted the manuscript, and decided to submit for publication. All authors reviewed, commented on, and approved this manuscript for publication.

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# Tables

**Table 1. Baseline Characteristics**

| | Placebo (n=131) | Auxora (n=130) | Total (N=261) |
|---|---|---|---|
| Male, n (%) | 92 (70.2%) | 84 (64.6%) | 176 (67.4%) |
| Race | | | |
| White, n (%) | 98 (74.8%) | 85 (65.4%) | 183 (70.1%) |
| Black, n (%) | 12 (9.2%) | 19 (14.6%) | 31 (11.9%) |
| Asian | 5 (3.8%) | 9 (6.9%) | 14 (5.4%) |
| Other/Multiple* | 16 (12.2%) | 16 (12.3%) | 32 (12.3%) |
| Hispanic, n (%) | 58 (44.3%) | 45 (34.6%) | 103 (39.5%) |
| Median age, years | 61 | 60 | 60 |
| 65+ years of age, n (%) | 47 (35.9%) | 45 (34.6%) | 92 (35.2%) |
| Median BMI, $kg/m^2$ | 31.0 | 31.1 | 31.0 |
| Median time from symptom onset, days | 12.0 | 11.0 | 12.0 |
| Median time from hospitalization to randomization, days | 3.0 | 3.0 | 3.0 |
| HFNC use, n (%) | 82 (62.6%) | 81 (62.3%) | 163 (62.5%) |
| Median baseline imputed $PaO_2/FiO_2$ value† | 104 | 106.7 | 106.7 |
| Imputed $PaO_2/FiO_2$ ≤100, n (%) | 58 (44.3%) | 59 (45.4%) | 117 (44.8%) |
| Imputed $PaO_2/FiO_2$ 101-200, n (%) | 73 (55.7%) | 71 (54.6%) | 144 (55.2%) |
| Median CRP, mg/L | 74.0 | 69.8 | 70.0 |
| Median ferritin, ng/mL | 780 | 764 | 773 |
| Hypertension, n (%) | 80 (61.1%) | 84 (64.6%) | 164 (62.8%) |
| Diabetes, n (%) | 57 (43.5%) | 52 (40.0%) | 109 (41.8%) |
| Hyperlipidemia, n (%) | 51 (38.9%) | 50 (38.5%) | 101 (38.7%) |
| Former smoker, n (%) | 34 (26.0%) | 39 (30.0%) | 73 (28.0%) |

*Other include Native Hawaiian or other Pacific Islander. One participant in the Auxora group was missing race at baseline; †Worst value in the 24 hours prior to Screening. BMI, body mass index; CRP, C-reactive protein; HFNC, high flow nasal cannula.

**Table 2: Primary and Secondary Endpoints.**

| | Placebo (n=131) | Auxora (n=130) | Difference (95% CI) | P Value |
|---|---|---|---|---|
| **Patients who recovered, n (%)** | 97 (74.0%) | 103 (79.2%) | | |
| **Median time to recovery, days (95% CI)** | 10.0 (7.0, 14.0) | 7.0 (6.0, 9.0) | | 0.0979 |
| **All-Cause Mortality at Day 60, n (%)** | 27 (20.6%) | 18 (13.8%) | -6.75 (-15.75, 2.24) | 0.1449 |
| **All-Cause Mortality at Day 30, n (%)** | 23 (17.6%) | 10 (7.7%) | -9.86 (-17.80, -1.93) | 0.0165 |
| **Invasive Mechanical Ventilation, Proportion of Patients Day 60 (95% CI)** | 0.28 (0.21, 0.37) | 0.19 (0.13, 0.28) | | 0.1882 |
| **Invasive Mechanical Ventilation or Death, Proportion of Patients Day 60 (95% CI)** | 0.31 (0.24, 0.39) | 0.23 (0.17, 0.31) | | 0.2994 |

Definition of Recovery by Ordinal Scale: 6 Hospitalized, not requiring supplemental oxygen or ongoing medical care; 7 Discharged, requiring supplemental oxygen; 8 Discharged, not requiring supplemental oxygen. Analysis of time to recovery through Day 60 in the efficacy set used log-rank test stratified by the baseline imputed $PaO_2/FiO_2$ ≤100 and 101-200; Analysis of all-cause mortality in the efficacy set used Cochran-Mantel-Haenszel test stratified by the baseline imputed $PaO_2/FiO_2$ ≤100 and 101-200

**Table 3: Primary and Key Secondary Endpoints by Oxygen Delivery Mode and Imputed $PaO_2/FiO_2$ at Baseline.**

| Oxygen Delivery at Baseline | | | | |
|---|---|---|---|---|
| **HFNC** | | | | |
| | **Placebo (n=82)** | **Auxora (n=81)** | **Difference (95% CI)** | **P Value** |
| **Patients who recovered, n (%)** | 54 (65.9%) | 62 (76.5%) | | |
| **Median time to recovery, days (95% CI)** | 17.0 (8.0, 30.0) | 9.0 (7.0, 13.0) | | 0.1079 |
| **All-Cause Mortality at Day 60, n (%)** | 21 (25.6%) | 13 (16.0%) | -9.36 (-21.79, 3.07) | 0.1436 |
| **Low Flow Oxygen** | | | | |
| | **Placebo (n=49)** | **Auxora (n=49)** | **Difference (95% CI)** | **P Value** |
| **Patients who recovered, n (%)** | 43 (87.8%) | 41 (83.7%) | | |
| **Median time to recovery, days (95% CI)** | 7.0 (5.0, 9.0) | 5.0 (4.0, 6.0) | | 0.4195 |
| **All-Cause Mortality at Day 60, n (%)** | 6 (12.2%) | 5 (10.2%) | -2.04 (-14.53, 10.45) | 0.7490 |
| **Imputed $PaO_2/FiO_2$ at Baseline** | | | | |
| **≤100** | | | | |
| | **Placebo (n=58)** | **Auxora (n=59)** | **Difference (95% CI)** | **P Value** |
| **Patients who recovered, n (%)** | 35 (60.3%) | 41 (69.5%) | | |
| **Median time to recovery, days (95% CI)** | 23.0 (11.0, 70.0) | 11.5 (8.0, 23.0) | | 0.1040 |
| **All-Cause Mortality at Day 60, n (%)** | 17 (29.3%) | 12 (20.3%) | -8.62 (-24.30, 7.06) | 0.2837 |
| **101-200** | | | | |
| | **Placebo (n=73)** | **Auxora (n=71)** | **Difference (95% CI)** | **P Value** |

| | | | | |
|---|---|---|---|---|
| **Patients who recovered, n (%)** | 62 (84.9%) | 62 (87.3%) | | |
| **Median time to recovery, days (95% CI)** | 7.0 (5.0, 8.0) | 6.0 (5.0, 7.0) | | 0.4156 |
| **All-Cause Mortality at Day 60, n (%)** | 10 (13.7%) | 6 (8.5%) | -5.25 (-15.45, 4.95) | 0.3164 |

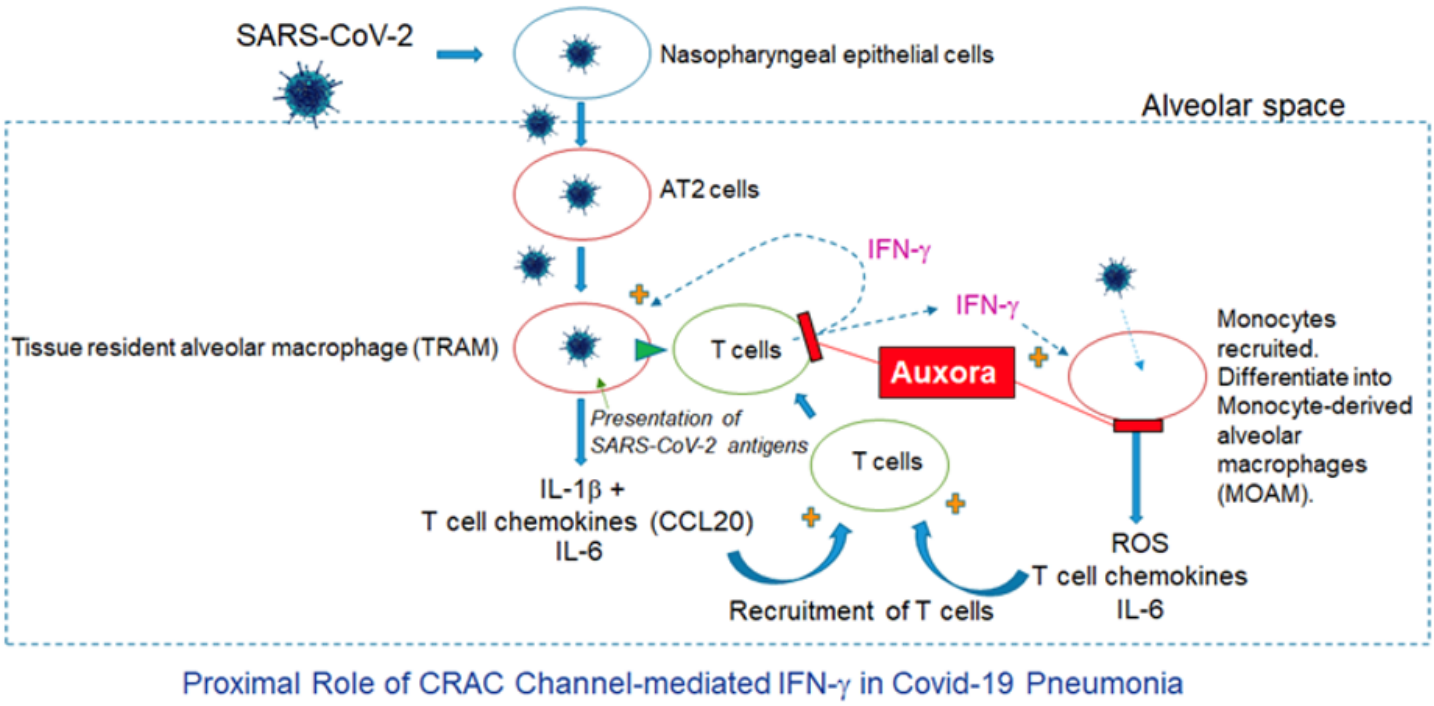
Definition of Recovery by Ordinal Scale: 6 Hospitalized, not requiring supplemental oxygen or ongoing medical care; 7 Discharged, requiring supplemental oxygen; 8 Discharged, not requiring supplemental oxygen. Kaplan-Meier estimate of Days to Recovery with P value based on log-rank test without stratification. Unstratified analysis of mortality using Chi-squared test. HFNC, high flow nasal cannula.

**Table 4. Safety Outcomes**

| | Placebo (n=140) | Auxora (n=141) |
|---|---|---|
| **Discontinuation Due to AE, n (%)** | 5 (3.6%) | 3 (2.1%) |
| **Serious Adverse Events ≥4%, n (%)** | | |
| **Respiratory Failure** | 26 (18.6%) | 22 (15.6%) |
| **ARDS** | 11 (7.9%) | 7 (5.0%) |
| **Pneumonia** | 7 (5.0%) | 6 (4.3%) |
| **Cardiac Arrest** | 6 (4.3%) | 6 (4.3%) |
| **Septic Shock** | 8 (5.7%) | 2 (1.4%) |
| **Most Common Treatment-Emergent Adverse Events ≥4%, n (%)** | | |
| **Respiratory Failure** | 26 (18.6%) | 22 (15.6%) |
| **Blood Triglycerides Increased** | 5 (3.6%) | 16 (11.3%) |
| **Hypertriglyceridemia** | 4 (2.9%) | 2 (1.4%) |
| **Hyperglycemia** | 11 (7.9%) | 11 (7.8%) |
| **Acute Kidney Injury** | 16 (11.4%) | 10 (7.1%) |
| **Increased Transaminases** | 5 (3.6%) | 8 (5.7%) |
| **Liver Function Test Increased** | 1 (0.7%) | 5 (3.5%) |
| **ARDS** | 11 (7.9%) | 7 (5.0%) |
| **DVT** | 7 (5.0%) | 7 (5.0%) |
| **Pneumonia** | 7 (5.0%) | 7 (5.0%) |
| **Pneumothorax** | 6 (4.3%) | 7 (5.0%) |
| **Pneumomediastinum** | 2 (1.4%) | 6 (4.3%) |
| **Hypoxia** | 7 (5.0%) | 6 (4.3%) |
| **Cardiac Arrest** | 6 (4.3%) | 6 (4.3%) |
| **Hyperkalemia** | 6 (4.3%) | 4 (2.8%) |
| **Anemia** | 9 (6.4%) | 3 (2.1%) |
| **Septic Shock** | 13 (9.3%) | 2 (1.4%) |

ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis.

# Figures

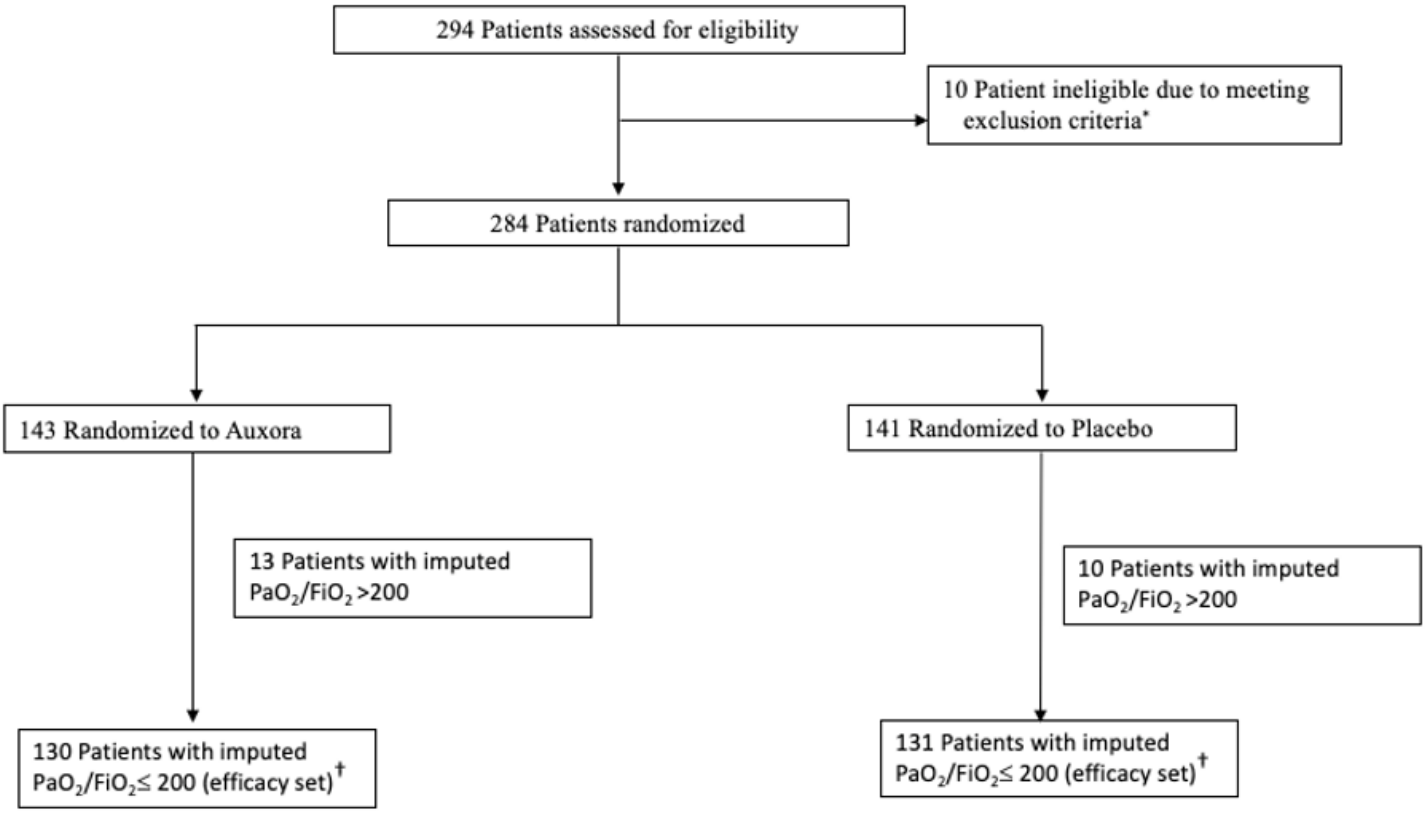



## Figure 1

### Proximal Role of CRAC Channel-mediated IFN-g in COVID-19 Pneumonia.

Tissue resident alveolar macrophages respond to SARS-CoV-2 infection in the lung by producing T-cell chemoattractants. Arriving T cells produce IFNg, leading to further alveolar macrophage activation and recruitment of monocyte-derived alveolar macrophages.[15,16] The feedback loop leads to a rapid increase in proinflammatory cytokines, diffuse alveolar injury, severe endothelialitis, ARDS, and multiorgan dysfunction and failure.[14,17,18] Auxora abrogates the release of multiple proinflammatory cytokines from human lymphocytes, including IL-6, IL-17, and IFNg that are implicated in COVID-19 alveolitis.[16,22] Adapted from Grant RA, et al. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature.* 2021;590(7847);635-641.

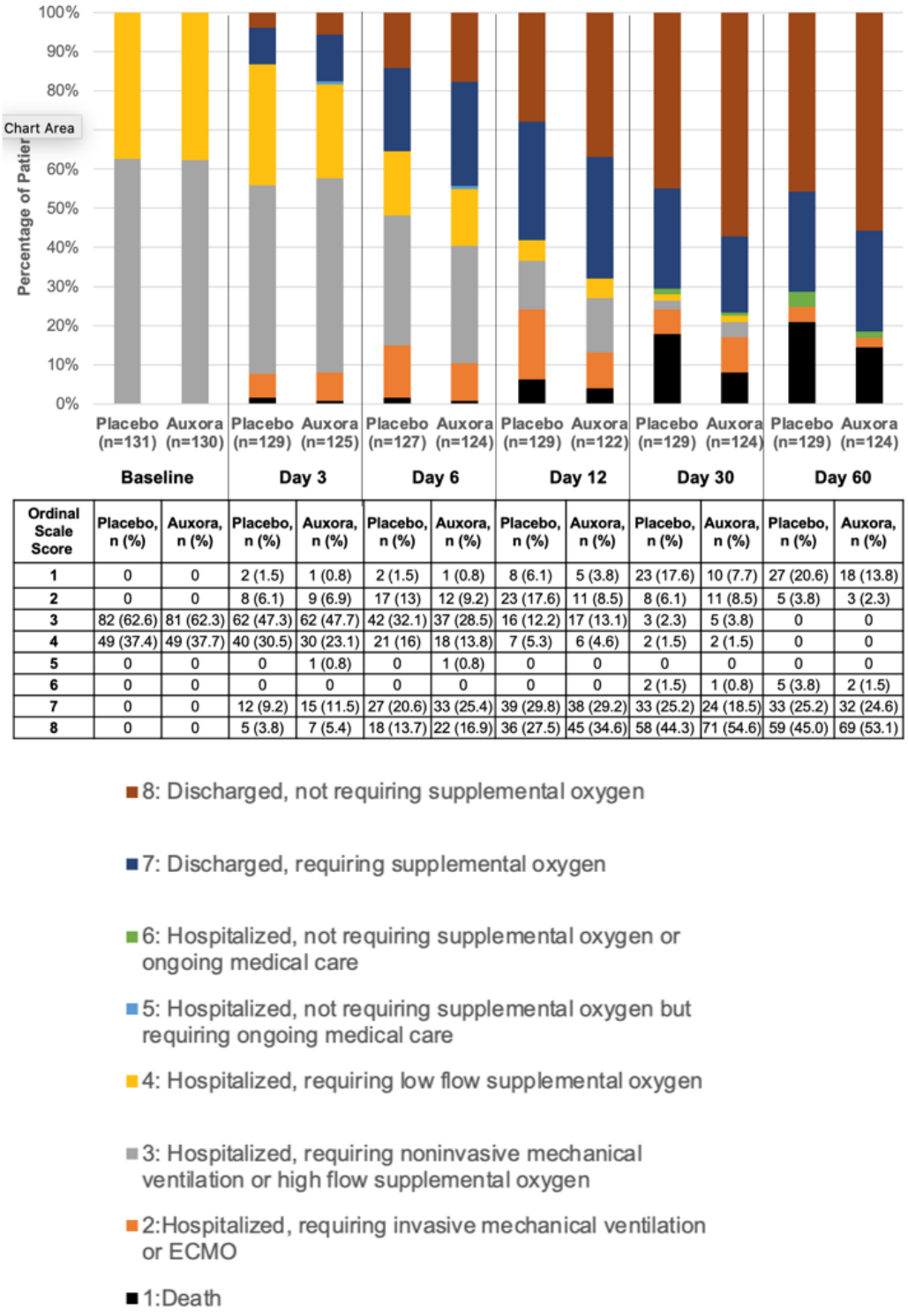
IL, interleukin; IFNg, interferon-gamma; ROS, reactive oxygen species.




## Figure 2

### Patient Enrolment and Randomization.

*Reasons for screen failure included $PaO_2/FiO_2$ £75 (n=3), at least 1 of the following signs at Screening or noted in the 24 hours before Screening: SpO2 <92% on room air; $PaO_2/FiO_2$ =300 when receiving low flow supplemental oxygen (n=3), do not intubate order (n=2), prohibited medication (n=1), history of organ or hematologic transplant, HIV, Active hepatitis B, or hepatitis C infection (n=1); †One patient in the Auxora arm and one patient in the placebo arm who had imputed $PaO_2/FiO_2$£ 200 at baseline did not receive any doses.




| Ordinal Scale Score | Placebo, n (%) | Auxora, n (%) | Placebo, n (%) | Auxora, n (%) | Placebo, n (%) | Auxora, n (%) | Placebo, n (%) | Auxora, n (%) | Placebo, n (%) | Auxora, n (%) | Placebo, n (%) | Auxora, n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 2 (1.5) | 1 (0.8) | 2 (1.5) | 1 (0.8) | 8 (6.1) | 5 (3.8) | 23 (17.6) | 10 (7.7) | 27 (20.6) | 18 (13.8) |
| 2 | 0 | 0 | 8 (6.1) | 9 (6.9) | 17 (13) | 12 (9.2) | 23 (17.6) | 11 (8.5) | 8 (6.1) | 11 (8.5) | 5 (3.8) | 3 (2.3) |
| 3 | 82 (62.6) | 81 (62.3) | 62 (47.3) | 62 (47.7) | 42 (32.1) | 37 (28.5) | 16 (12.2) | 17 (13.1) | 3 (2.3) | 5 (3.8) | 0 | 0 |
| 4 | 49 (37.4) | 49 (37.7) | 40 (30.5) | 30 (23.1) | 21 (16) | 18 (13.8) | 7 (5.3) | 6 (4.6) | 2 (1.5) | 2 (1.5) | 0 | 0 |
| 5 | 0 | 0 | 0 | 1 (0.8) | 0 | 1 (0.8) | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (1.5) | 1 (0.8) | 5 (3.8) | 2 (1.5) |
| 7 | 0 | 0 | 12 (9.2) | 15 (11.5) | 27 (20.6) | 33 (25.4) | 39 (29.8) | 38 (29.2) | 33 (25.2) | 24 (18.5) | 33 (25.2) | 32 (24.6) |
| 8 | 0 | 0 | 5 (3.8) | 7 (5.4) | 18 (13.7) | 22 (16.9) | 36 (27.5) | 45 (34.6) | 58 (44.3) | 71 (54.6) | 59 (45.0) | 69 (53.1) |

## Figure 3

### Proportion of Patients in Each Ordinal Scale Category Over Time.

A higher proportion of patients receiving Auxora were discharged, and a lower proportion progressed to invasive mechanical ventilation, ECMO, and death at Day 60 (Odds Ratio, 0.647; 95% CI 0.405, 1.031; *P*=0.0672) and Day 30 (Odds Ratio, 0.617; 95% CI 0.387, 0.983; *P*=0.0423). 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. The proportions are compared between the two treatment groups using a proportional odds model with a fixed factor of treatment groups.

ECMO, Extracorporeal membrane oxygenation

## Supplementary Files

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

- SupplementalappendixAuxorainCOVID19CritCare06Jan2022Final.docx