**Supplemental appendix**

**Auxora vs. placebo for the treatment of patients with severe COVID-19 pneumonia: a randomized clinical trial**

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**Inclusion Criteria**

All of the following must be met for a patient to be randomized into the study:

* Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay in any specimen, as documented by either of the following: o PCR positive in sample collected < 72 hours prior to randomization; or
  + PCR positive in sample collected ≥ 72 hours prior to randomization, with inability to obtain a repeat sample (e.g. due to lack of testing supplies, or limited testing capacity, or results taking >24 hours, etc.) or progressive disease suggestive of ongoing SARS-CoV-2 infection;
* At least 1 of the following symptoms:
  + Fever, cough, sore throat, malaise, headache, muscle pain, dyspnea at rest or with exertion, confusion, or respiratory distress;
* At least 1 of the following signs at Screening or noted in the 24 hours before Screening:
  + PaO2/FiO2 ≤200 when receiving supplemental oxygen. The PaO2/FiO2 may be estimated from pulse oximetry or determined by arterial blood gas;
  + If SpO2 ≥97%, receiving 10L or more of supplemental oxygen;
* The presence of a respiratory infiltrate or abnormality consistent with pneumonia that is documented by either a CXR or CT scan of the lungs;
* The patient is ≥18 years of age;
* A female patient of childbearing potential must not attempt to become pregnant for 39 months, and if sexually active with a male partner, is willing to practice acceptable methods of birth control for 39 months after the last dose of study drug;
* A male patient who is sexually active with a female partner of childbearing potential is willing to practice acceptable methods of birth control for 39 months after the last dose of study drug. A male patient must not donate sperm for 39 months;
* The patient is willing and able to, or has a legal authorized representative (LAR) who is willing and able to, provide informed consent to participate, and to cooperate with all aspects of the protocol.

**Exclusion Criteria**

Patients with any of the following conditions or characteristics must be excluded from randomizing:

* Expected survival or time to withdrawal of life-sustaining treatments expected to be <7 days;
* Do Not Intubate order;
* Home mechanical ventilation (noninvasive ventilation or via tracheotomy) except for continuous positive airway pressure or bi-level positive airway pressure (CPAP/BIPAP) used solely for sleep-disordered breathing;
* PaO2/FiO2 ≤75 at the time of Screening. The PaO2/FiO2 may be estimated from pulse oximetry or determined by arterial blood gas;
* Noninvasive positive pressure ventilation;
* Invasive mechanical ventilation via endotracheal intubation or tracheostomy;
* ECMO;
* Shock defined by the use of vasopressors;
* Multiple organ dysfunction or failure;
* Positive Influenza A or B testing if tested as local standard of care;
* The patient has a history of:
  + Organ or hematologic transplant;
  + HIV
  + Active hepatitis B, or hepatitis C infection;
* Current treatment with:
  + Chemotherapy;
  + Immunosuppressive medications or immunotherapy at the time of consent;
  + Hemodialysis or Peritoneal Dialysis;
* Have a history of venous thromboembolism (VTE) (deep vein thrombosis [DVT] or pulmonary embolism [PE]) within 12 weeks prior to screening or have a history of recurrent (> 1) VTE;
* The patient is known to be pregnant or is nursing;
* Currently participating in another study of an investigational drug or therapeutic medical device at the time of consent;
* Allergy to eggs or any of the excipients in Auxora.

# Figure S1. All-Cause Mortality Through Day 60 (Efficacy Set).

The all-cause mortality rate at Day 60 was 0.21 (95% CI 0.15–0.29) for placebo and 0.12 (95% CI 0.08–0.19) for Auxora when estimated by the Kaplan-Meier procedure (*P*=0.0730). P-value is based on the stratified Kaplan-Meier estimates and standard errors estimated by Greenwood formula using the log-log transformation of the survival function stratified by the baseline imputed PaO2/FiO2 of ≤100 vs 101-200.Chart, line chart

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# Figure S2. All-Cause Mortality at Day 60 for Patients Requiring High Flow Supplemental Oxygen at Baseline (Efficacy Set).

The all-cause mortality rate at Day 60 was 0.26 (95% CI, 0.18–0.37) for placebo and 0.15 (95% CI, 0.09–0.25) for Auxora when estimated by the Kaplan-Meier procedure (*P*=0.0980). *P*-value is based on the Kaplan-Meier estimates and standard errors estimated by Greenwood formula using the log-log transformation of the survival.

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# Figure S3. All-Cause Mortality at Day 60 for Patients with Imputed PaO2/FiO2 ≤100 at Baseline (Efficacy Set).

The all-cause mortality rate at Day 60 was 0.29 (95% CI, 0.19–0.43) for placebo and 0.19 (95% CI, 0.11–0.32) for Auxora when estimated by the Kaplan-Meier procedure (*P*=0.1958). *P*-value is based on the Kaplan-Meier estimates and standard errors estimated by Greenwood formula using the log-log transformation of the survival.

![Chart

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# Figure S4. Subgroup Analysis of All-Cause Mortality at Day 60 (Efficacy Set).

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# Table S1: Concomitant Medications for COVID-19 (Efficacy Set).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Placebo  (n=131) | Auxora  (n=130) | Total  (n=261) |
| Corticosteroids | 131 (100%) | 130 (100%) | 261 (100%) |
| Dexamethasone | 111 (84.7%) | 113 (86.9%) | 224 (85.8%) |
| Methylprednisolone | 43 (32.8%) | 37 (28.5%) | 80 (30.7%) |
| Prednisone | 17 (13%) | 13 (10%) | 30 (11.5%) |
| Remdesivir | 94 (71.8%) | 104 (80.0%) | 198 (75.9%) |
| Anticoagulation | 130 (99.2%) | 130 (100%) | 260 (99.6%) |
| Enoxaparin | 118 (90.1%) | 125 (96.2%) | 243 (93.1%) |
| Tocilizumab | 6 (4.6%) | 2 (1.5%) | 8 (3.1%) |
| Hyperimmune Plasma COVID-19 | 2 (1.5 %) | 1 (0.8%) | 3 (1.1%) |

# Table S2: Baseline Characteristics (All Randomized Patients).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Placebo  (n=141) | Auxora  (n=143) | Total  (N=284) |
| Male, n (%) | 99 (70.2%) | 91 (63.6%) | 190 (66.9%) |
| Race |  |  |  |
| White, n (%) | 104 (73.8%) | 93 (65.0%) | 197 (69.4%) |
| Black, n (%) | 14 (9.9%) | 22 (15.4%) | 36 (12.7%) |
| Asian | 5 (3.5 %) | 9 (6.3 %) | 14 (4.9%) |
| Other/Multiple\* | 18 (12.8 %) | 18 (12.6 %) | 36 (12.7%) |
| Hispanic, n (%) | 59 (41.8%) | 49 (34.3%) | 108 (38.0%) |
| Median age, years | 60 | 60 | 60 |
| 65+ years of age, n (%) | 50 (35.5%) | 48 (33.6%) | 98 (34.5%) |
| Median BMI, kg/m2 | 30.9 | 30.8 | 30.9 |
| Median time from symptom onset, days | 12.0 | 11.0 | 11.0 |
| Median time from hospitalization to randomization, days | 3.0 | 3.0 | 3.0 |
| HFNC use, n (%) | 83 (58.9%) | 81 (56.6%) | 164 (57.7%) |
| Median baseline imputed PaO2/FiO2 value† | 106.8 | 111.7 | 109.8 |
| Imputed PaO2/FiO2 ≤100, n (%) | 58 (41.1%) | 59 (41.31%) | 117 (41.2%) |
| Imputed PaO2/FiO2 101-300, n (%) | 83 (58.9%) | 84 (58.7%) | 167 (58.8%) |
| Median CRP, mg/L | 74.5 | 73.0 | 74.0 |
| Median ferritin, ng/mL | 775 | 752 | 756.5 |
| Hypertension, n (%) | 86 (61.0%) | 90 (62.9%) | 176 (62.0%) |
| Diabetes, n (%) | 61 (43.3%) | 60 (42.0%) | 121 (42.6%) |
| Hyperlipidemia, n (%) | 57 (40.4%) | 56 (39.2%) | 113 (39.8%) |
| Former smoker, n (%) | 36 (25.5%) | 45 (31.5%) | 81 (28.5%) |

\*Other include Native Hawaiian or other Pacific Islander. One participant in the Auxora arm 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 S3. Primary and Key Secondary Endpoints (All Randomized Patients).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Placebo  (n=141) | Auxora  (n=143) | Difference  (95% CI) | P Value |
| Patients who recovered, n (%) | 107 (75.9%) | 115 (80.4%) |  |  |
| Median time to recovery, days (95% CI) | 8.0  (7.0, 11.0) | 7.0  (6.0, 8.0) |  | 0.0533 |
| All-Cause Mortality at Day 60, n (%) | 27 (19.1%) | 18 (12.6%) | -6.43  (-14.74, 1.88) | 0.1321 |

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 PaO2/FiO2 ≤100 and 101-200; Analysis of all-cause mortality in the efficacy set used Cochran-Mantel-Haenszel test stratified by the baseline imputed PaO2/FiO2 ≤100 and 101-200.

# Table S4: Number of Hospitalized Days or ICU Days During the First 28 Days of the Study (Efficacy Set).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Placebo (n=131) | Auxora  (n-130) | Difference (95% CI; P value) |
| Hospitalized Days | LS Mean | 15.29 | 13.65 | -1.64 (-4.09–0.80; 0.1864) |
| ICU Days | LS Mean | 8.36 | 6.88 | -1.47 (-4.25–1.30; 0.2970) |

ANOVA model includes treatment group as fixed effect in the model. The number of days in the hospital is defined as 28 if the patient died. ICU, intensive care unit.