A Trial of Aclaris Therapeutics, Inc. (ATI)-450 in Patients With Moderate-severe Novel Coronavirus Disease 2019 (COVID-19)

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# Statistical Analysis Plan

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| **Study Title:** | A double-blind, randomized, controlled trial of ATI-450 in patients with moderate-severe COVID-19 |
| **Phase:** | 2A |
| **Protocol No.:** | IIT-2020-ATI-450-COVID-19 |

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol IIT-2020-ATI-450-COVID-19 by the Department of Biostatistics and Data Science of the University of Kansas Medical Center based on the criterion for investigator-initiated trails (IITs) of KUMC.

## Study Overview

IIT-2020-ATI-450-COVID-19 is a Phase 2A, double-blinded, randomized, placebo-controlled, proof of concept, safety, efficacy, multi-center study of ATI-450 as monotherapy for treating patients with moderate to severe COVID-19 disease.

Patients who have laboratory-confirmed COVID-19 as determined by polymerase chain reaction (PCR), or other commercial or public health assay in oropharyngeal or nasopharyngeal testing within 14 days of hospitalization, and are currently hospitalized as a result of symptoms and signs related to COVID-19 pneumonia with evidence of hypoxic respiratory failure: pulse oximeter measurement of oxygen saturation (SpO2) $\leq$93%, or SpO2 >93% requiring $\geq$ 2L of supplement oxygen (O2), or partial pressure of oxygen (PaO2)/ fraction of inspired oxygen (FiO2) ratio <300mmHg, or tachypnea (respiratory rate > 30 breaths/min) or evidence of pulmonary involvement by chest imaging or pulmonary exam will be eligible for enrollment into the study. Eligible patients will be randomized in a 1:1 ratio to either 50 mg oral ATI-450 twice daily (BID) or placebo BID for 14 days or until patient discharge whichever is earlier.

### Treatment Assignment:

A total of approximately 20 patients will be randomized in a 1:1 ratio:

- Placebo oral tablet BID for 14 days
- ATI-450 oral tablet, 50 mg, BID for 14 days

Survival follow up assessments will be conducted 28-, 45- and 60-Days post hospital Day-1 and all participants should complete these visits. Exceptions include death, lost to follow-up or the participant withdrawing consent for follow-up all of which should be documented in the participants medical record and EDC.

## Study objectives

### Primary Objective:

The primary objective is to assess the efficacy of ATI-450 on hypoxic respiratory failure-free survival in patients with moderate-severe COVID-19 pneumonia at day 14.

**Secondary Objectives:**

- To assess the clinical efficacy of ATI-450 on respiratory function and survival in patients with moderate-severe COVID-19 pneumonia.
- To assess the safety of ATI-450 in patients with moderate-severe COVID-19 pneumonia.

**Exploratory Objectives:**

- To Assess the pharmacodynamics of ATI-450 in patients with moderate-severe COVID-19 pneumonia.

## Outcome Measures

**Primary Efficacy Measure**

- Primary treatment responder: defined as any patient who is alive, free of respiratory failure (does not require supplemental oxygen (greater than pre-exising use)) and does not experience a negative intercurrent event on Day 14 of the trial.

  An intercurrent event is one that occurs after the first dose of study medication and either precludes the observation of the primary variable/endpoint or affects its interpretation. The following is a list of negative intercurrent events that could occur during this study:

  - Death
  - Withdrawal from study
  - Intubation and ventilation
  - Rescue with a non-protocol specified treatment for cytokine release syndrome

  The following is a list of positive intercurrent events that could occur during this study:

  - Early hospital discharge due to recovery

  A patient will be considered a treatment responder if the primary endpoint is missing following a positive intercurrent event. A patient will be considered a treatment non-responder for all observations (missing or not missing) following a negative intercurrent event.

**Secondary Efficacy Measures**

- Change from baseline in the WHO COVID-19 7-point ordinal scale over time (BASELINE, DAY 7, DAY 14, DAY 28).
- All-cause mortality through Day 60 (DAY 7, DAY 14, DAY 28 AND FOLLOW-UP.).
- Responder based on 7-point ordinal scale: Greater than 2-point improvement from baseline on the 7-point ordinal scale. (BASELINE, DAY 7, DAY 14, DAY 28 AND FOLLOW-UP.).
- Time to discharge from the hospital.

**Safety assessments include:**

- Adverse events

**Exploratory measures include:**

- Change in serum cytokine Interleukin (IL)-6 over time (baseline, d7, EOT, d28).
- Change in serum cytokine IL-8 over time (baseline, d7, EOT, d28).
- Change in serum cytokines IL-1β over time (baseline, d7, EOT, d28).
- Change in serum cytokine Tumor Necrosis Factor (TNF-α) over time.
  *EOT: end of treatment

## Sample Size Justification

Data from 20 patients (10 randomized to ATI-450 and 10 to Placebo) provide some preliminary information about the efficacy and safety of ATI-450. No hypothesis will be formally tested. The mean and exact 90% confidence intervals for within-group event rates will be estimated and no between group difference will be estimated.

## Randomization and Blinding

Prior to the start of the study, the University of Kansas Medical Center will generate a list of randomization numbers that shall be transmitted to the assigned clinical packaging organization for study medication labeling. The randomization list will be stored with access limited to designated personnel for study medication labeling. The randomization list will be made available, as appropriate, to unblind the database.

In the treatment period, subjects will be assigned to 1 of the 2 treatment groups in a random manner and at a 1:1 ratio stratified by baseline age group (<60 versus ≥ 60). At the Day 1 visit an investigational center staff member will assign study medication to eligible subjects by selecting an appropriate Subject Kit. The staff member must select Subject Kits in chronological sequence and in an ascending numerical order starting with the lowest available Subject Kit number. No Subject Kit number may be omitted or reused. The Subject Kit number is the randomization number.

This study uses a double-blind design. The study medications are indistinguishable in appearance, as packaged and labeled.

**Analysis populations**

- The Full Analysis Set (FAS) will include all patients who have been administered at least one dose of study medication. The FAS will be population used in the primary efficacy analysis. The FAS will also be the population used secondary efficacy analyses and summaries as well as the population used in all safety summaries. The FAS will be analyzed/summarized as randomized when applied to efficacy endpoints. The FAS will be analyzed/summarized as treated when applied to safety endpoints.
- The Per-Protocol population will include all FAS patients who have completed their Day 14 visit and have continued study drug administration through Day 14 or were successfully discharged prior to Day 14. The Per-protocol population will be used for the primary efficacy analysis. Summaries and analyses using the per-protocol population will be done as treated.

**Statistical Analysis Methods**

Descriptive statistics (number of observations, mean (standard deviation) or median (minimum, maximum) ) will be provided for continuous variables, and counts and percentages will be presented for categorical variables for each group.

**Primary Efficacy Analysis**

The study is hypothesis generating. The primary assessment of efficacy for this study will be the point estimate and corresponding exact 90% confidence interval for the proportions of responders for the ATI-450 and Placebo groups. All subjects who are alive, free of respiratory failure (do not require supplemental oxygen) by Day 14 of the trial will be considered responders. The point estimate and corresponding 90% confidence interval will be derived based on sample proportions and the Copper-Pearson CIs for proportions for the two groups (categorical data analysis by Alan Agresti, 3rd edition).

**Secondary Efficacy Analyses**

Binary variables will be analyzed using the method like that described for the primary endpoint. In addition to the point estimate and confidence interval for the difference in proportions for binary endpoints, odds ratios, corresponding confidence intervals will be provided. For binary measures that are recorded over time, separate analyses will be conducted at each timepoint.

Continuous secondary efficacy endpoints will be analyzed by estimating group means and mean difference and 95% CIs at each time point. Missing data will be imputed with the single imputation methods described above (LOCF or WOCF).

For time to discharge from hospital, estimates of the median (50th percentile) will be provided for each treatment group and Kaplan-Meier Curves will be provided. A two-sided stratified log-rank test will be applied. The stratification factor will be baseline age group (<60 versus >= 60).

**Exploratory Outcomes Analyses**

For all the Cytokines, changes over time (baseline, d7, EOT, d28) will be summarized by descriptive statistics and trajectory plots. Any time point after the end of treatment (EOT) will not be measured.

**Safety Summaries**

AEs will be summarized using table format based on DSMB requirements (attached).

## Missing Data Imputation

Missing data for binary secondary endpoints will be treated in a similar manner as the primary endpoint. For secondary endpoints of a continuous nature, the last observation prior to the intercurrent event will be carried forward (LOCF) for all positive intercurrent events and the worst observation prior to the intercurrent event will be carried forward (WOCF) for all negative intercurrent events.

Primary efficacy analysis will be done on the Full Analysis Set (FAS) and the per protocol population. Secondary efficacy analyses and safety analysis will be done on FAS only.

The statistical analyses and summaries will be conducted with the SAS® software package version 9.4 or higher.

**Attachments:**

- *IIT-2020-ATI-450-COVID-19 _DSMB_AdverseEventListingShell.xls*
- *IIT-2020-ATI-450-COVID-19 DSMB ReportTableShells_2020_1008.doc*