Investigator Initiated Trial

A double-blind, randomized, controlled trial of ATI-450 in patients with moderate-severe COVID-19

SPONSOR/INVESTIGATOR

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Agents: ATI-450

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LIST OF COLLABORATORS

Name	Affiliation	Role
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Participating Sites:
The University of Kansas Medical Center (KUMC)

STATEMENT OF COMPLIANCE / PROTOCOL AGREEMENT

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Protocol Number	IIT-2020-ATI-450-COVID-19
Protocol Title	*A double-blind, randomized, controlled trial of ATI-450 in patients with moderate-severe COVID-19 pneumonia*
Sponsor/Investigator	Gregory Gan, MD, PhD
Co-Principal Investigator	Deepika Polineni, MD, MPH

Signature of Lead Principal Investigator Date

Printed Lead Principal Investigator Name

Institution Name

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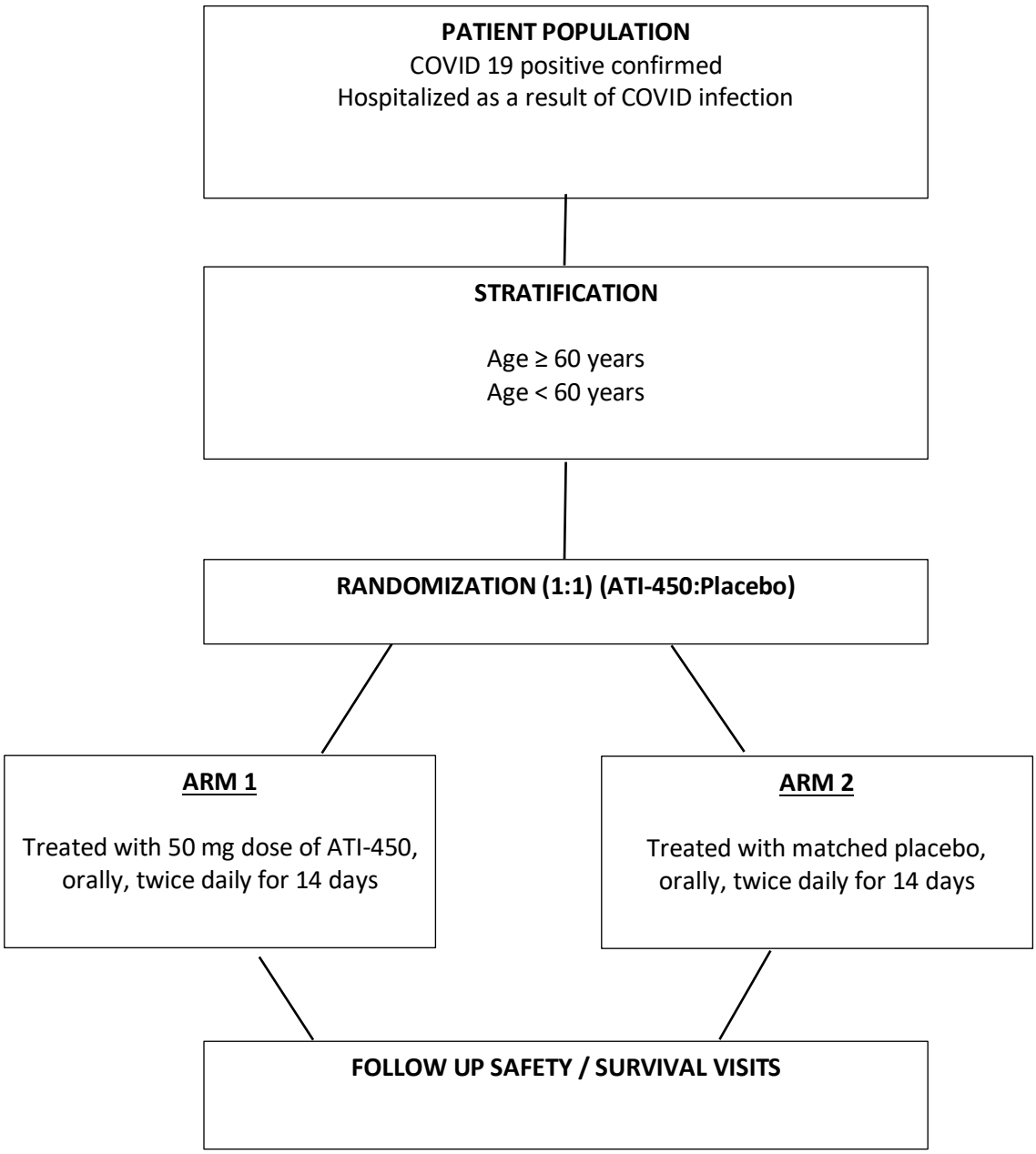


PROTOCOL SUMMARY

Title	A double-blind, randomized controlled trial of ATI-450 in patients with moderate-severe COVID-19
Protocol Number	IIT-2020-ATI-450-COVID-19
Phase	2a
Design	Phase 2a, randomized, double-blind, placebo controlled, parallel group study in patients with moderate to severe COVID-19
Study Duration	9 months
Study Center(s)	The University of Kansas Medical Center
Objectives	**Primary Objective** To assess the efficacy of ATI-450 on hypoxic respiratory failure-free survival in patients with moderate-severe COVID-19 **Secondary Objectives** To assess the clinical efficacy of ATI-450 on respiratory function and survival in patients with moderate-severe COVID-19 To assess the anti-inflammatory and immune effect of ATI-450 To assess the safety of ATI-450 in patients with moderate-severe COVID-19 **Exploratory Objective** To assess the pharmacodynamics of ATI-450 in patients with moderate-severe COVID-19
Number of Participants	20
Diagnosis and Main Inclusion Criteria	Has laboratory-confirmed COVID-19 coronavirus infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in nasopharyngeal testing within 14 days of enrollment AND, Hospitalized as a result of symptoms and signs related to COVID-19 infection, and ≤14 days since positive test AND: Evidence of hypoxic respiratory failure: SpO2 ≤93% on room air or supplemental oxygen, or SpO2 ≥93% requiring ≥ 2L O2, or PaO2/FiO2 ratio <300mmHg, or tachypnea (respiratory rate ≥ 30 breaths/min) and Evidence of pulmonary involvement by chest imaging or pulmonary exam
Study Product(s), Dose, Route, Regimen	**Dose of ATI-450** 50 mg (as determined from Phase I study) per dose. (100 mg per day). or Placebo

	Route Oral tablet **Schedule** Pill will be taken twice daily preferably spaced 12 ±1 hours apart.
Duration of Administration	Up to a maximum of 14 days while inpatient. Patients discharged home or new requirement for mechanical ventilation will be discontinued off drug permanently.
Interim Monitoring	The study will be monitored at appropriate intervals, no less than those assigned per risk level designation, to assure compliance to GCP and to assess the data quality and study integrity.
Statistical Methodology	Details of the statistical analyses and summaries will be provided in the study-specific statistical analysis plan (SAP). **Determination of Sample Size** Data from 36 patients (18 randomized to ATI-450 and 18 to Placebo) provide enough precision to ensure that the expected asymmetric 70% confidence interval for the difference in the proportion of responders will be no wider than 31 percentage points. This level of precision for the planned 70% confidence interval will facilitate development decisions in accordance with the methods of Frewer et al.[1] **Analysis Populations** • The Full Analysis Set (FAS) will include all patients who have been administered at least one dose of study medication. • 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 discharged with a successful outcome prior to day 14. **Efficacy Analyses and Summaries** Primary Efficacy Analysis The primary assessment of efficacy for this study will be the point estimate and corresponding asymmetric 70% confidence interval for the difference in proportions of responders between the ATI-450 and Placebo groups. All subjects who are alive, free of respiratory failure (do not require supplemental oxygen) and do not experience negative intercurrent events by Day 14 of the trial will be considered responders. The point estimate and corresponding 70% confidence interval will be derived using a logistic regression model that includes treatment group, baseline age group (<60 versus ≥60), and gender as factors. Secondary Efficacy Analyses Supportive analyses will be conducted on the secondary efficacy endpoints described in Section 3.5. Categorical variables will be analyzed using a logistic regression similar to that described for the primary

	endpoint. In addition to the point estimate and confidence interval for the difference in proportions for categorical endpoints, odds ratios, corresponding confidence intervals and p-values will be provided. For categorical measures that are recorded over time, separate logistic regression analyses will be conducted at each timepoint. For continuous secondary efficacy endpoints, a mixed model repeated measures MMRM analysis will be conducted. The MMRM will include factors for treatment, baseline age group, gender, and scheduled timepoint as well as a random effect for patient. Model based means for each treatment group and the difference between treatment groups will be provided as well as corresponding confidence intervals and p-values. For time-to-event data, a two-sided stratified log-rank test will be applied. The stratification factor will be baseline age group (<60 versus ≥60). Estimates of the 25th, 75th percentile and the median (50th percentile) will be provided for each treatment group. Kaplan-Meier Curves and corresponding 95% confidence intervals will be provided as well as p-values based on the stratified log-rank test. **Safety Summaries** The FAS population will be used for the analysis of safety data (AEs, exposure to study medication, clinical laboratory values, vital signs, and ECG). AEs will be coded with the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the date of first administration of study medication and before the date of last administration of study medication + 30 days. TEAEs will be presented by system organ class and preferred term in frequency tables. Patients with multiple AEs will be counted only once within each preferred term and system organ class. Key patient information for patients with an AE with an outcome of death, patients with SAEs, and patients with an AE leading to discontinuation of study medication will be listed. Laboratory data (hematology, serum chemistry, coagulation, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively. Laboratory data outside study specific reference ranges will be listed. Vital signs and ECG parameters will be presented descriptively
Stopping Rules	Development of drug-related bacterial or fungal infection Full list in 11.2 and 11.4

1 INTRODUCTION

1.1 Background

1.1.1 COVID-19 PANDEMIC

The novel coronavirus disease 2019 (COVID-19) is a rapidly spreading global viral pandemic which exhibits a high-risk of mortality in selected populations (i.e. elderly, immunocompromised, cardiopulmonary diseases). As of 4/6/20, there are over 347,000 COVID-19 positive patients diagnosed in the US with over 10,000 deaths attributed to this disease (Johns Hopkins University COVID-19 Map).[2] Acute respiratory distress syndrome (ARDS) is associated with severe cases of COVID-19 and is often fatal in high risk populations.[3] A hyperinflammatory state caused by excessive inflammatory cytokine production (i.e. tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), granulocyte colony stimulating factor (G-CSF)) has been attributed to the pathobiology of ARDS[4] and results from China identified in patients severely affected and/or who died from COVID-19 had elevated levels of inflammatory factors (i.e. D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP)) and inflammatory cytokines (i.e. IL-1 β , IL-2, IL-6, IL-8, TNF α , MIP1 α , G-CSF).[5,6]

1.1.2 MAPK PATHWAY AND INFLAMMATION

Inflammation and inflammatory disorders signal primarily through the MAPK pathway. Activation of p38α is mediated by the TLR4/LPS signaling axis and is important for regulating inflammation[7,8,9] and aberrant p38α activation is associated in the pathobiology of diseases such as idiopathic pulmonary fibrosis (IPF), rheumatoid arthritis (RA), chronic obstructive pulmonary disease and tissue fibrosis.[10,11,12,13,14,15] Multiple labs have shown that the downstream target of p38α is the protein MAPKAPK2 (MK2) and is responsible for post-transcriptional production of pro-inflammatory cytokines such as IL-1α , IL-1 β, IL-6, TNFα , and G-CSF[16,17,18,19,20] – the same cytokines elevated in COVID-19 inflammation. Further evidence in other severe viral illnesses (i.e. Dengue, Influenza, CMV) show activation of p38-MK2 signaling axis for mediating inflammation.[21,22,23] Potentially, COVID-19 mediated inflammatory cytokine production may signal through p38α -MK2 axis and MK2 pathway blockade may suppress unwanted inflammation. A new group of drugs which target MK2 have demonstrated pre-clinical efficacy at suppressing inflammatory cytokine production and reduced tissue fibrosis[24,25,26,27,28]; and has demonstrated clinical safety in multiple Phase I clinical studies that included smokers in one study and[29,30] another unpublished Phase I study performed by Aclaris Pharmaceuticals, Inc, examining an oral inhibitor of MK2 performed in healthy subjects has similarly demonstrated clinical safety and tolerability. However, it remains unknown whether reducing the inflammatory state can improve COVID-19 patient outcomes.

1.1.3 MAPKAPK2 (MK2) AND ATI-450

Aclaris Therapeutics, Inc. is developing ATI-450, an orally available, small molecule inhibitor of the p38α mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) inflammatory signaling pathway. This pathway drives the expression of multiple cytokines, chemokines, matrix metalloproteases, and other inflammatory signals. Key inflammatory cytokines driven by this pathway include TNF-, IL-1 α, IL-1β, IL-6, IL-8, G-CSF.

ATI-450 has a novel mechanism of action. It targets the high affinity docking interaction between p38α MAPK and MK2. Upon binding to the interface created upon formation of this bimolecular complex, ATI-450 blocks MK2 phosphorylation by p38MAPK and thereby the downstream MK2-mediated inflammatory pathway. ATI-450 shows low potency for inhibition of p38α phosphorylation/activation of alternate substrates and is selective across the human kinome.

1.1.4 PRE-CLINICAL EXPERIENCE WITH ATI-450

1.1.4.1 PRE-CLINICAL PHARMACOLOGY

ATI-450 was developed to selectively block p38α activation of the proinflammatory kinase MK2 while sparing inhibition of p38α alone or other substrates such as p38α-related/activated protein kinase (PRAK) and activating transcription factor 2 (ATF2). The activity and selectivity of ATI-450 has been measured in a variety of in vitro assays, including functional assays directly measuring the phosphorylation of MK2. In all assays, ATI-450 showed high potency and, at high concentrations, resulted in full blockade of measured response.

ATI-450 reduced lipopolysaccharide (LPS)-induced production of TNF-α and IL-6 in vivo rat and mouse models. Oral administration of 1 mg/kg of ATI-450 resulted in ≥80% inhibition of LPS-induced TNF-α and IL-6 levels in rats. Oral administration (1000 ppm dietary admixture) of ATI-450 to mice for 3 days prior to the investigational product challenge with LPS (0.5 mg/mouse) resulted in >87% inhibition of circulating TNF-α levels. Inhibition was maintained in mice treated for up to 4 weeks.

To determine whether p38α-MK2 regulates inflammasome priming signals, neonatal-onset multisystem inflammatory disease (NOMID) mice, expressing consecutively activated NLRP3 in myeloid cells driven by lysozyme M-Cre were used. The phenotype of these mice resembles that of mice globally expressing a NLRP3 mutant, although the disease is less severe in mice with myeloid-restricted expression of the transgene. LPS markedly induced IL-1β, IL-6, and TNF-α expression in wild-type and NOMID bone marrow macrophages; these responses correlated with p38α and MK2 activation and were inhibited by ATI-450. MK2 phosphorylation peaked at 30 minutes before returning to baseline levels 180 minutes after stimulation. ATI-450 inhibited the transient LPS-stimulated MK2 phosphorylation at 15 and 30 minutes but had little effect at 180 minutes when MK2 activation returned to baseline state. ATI-450 was not cytotoxic at an efficacious concentration tested in the study.

1.1.4.2 PRE-CLINICAL PHARMACOKINETICS AND METABOLISM

The pharmacokinetics (PK) of ATI-450 was studied in mouse, rat, dog, monkey, and mini-pigs. The single dose intravenous PK in all nonclinical species is characterized by a mono-exponential pattern of elimination with mean half-lives ranging from 0.5 to 3.1 hours. After oral dosing, the mean half-life was observed to be up to 6.33 hours in the monkey. Clearance was low in dog and monkey and high in rat and mouse. Oral bioavailability was high in mouse; moderate in rat, dog, and monkey; and lower in mini-pig.

ATI-450 has the potential to translate the observed pre-clinical efficacy into the clinic based upon its oral drug-like properties. Metabolic stability and PK properties of ATI-450 (e.g., long half-life, low clearance, high oral bioavailability, high volume of distribution) are consistent with oral, 1 to 2 times per day dosing in humans.

1.1.4.3 TOXICOLOGY AND SAFETY PHARMACOLOGY

In vitro, no appreciable off-target interactions were observed in broad profile screening against receptors, enzymes, and transporters relevant for safety evaluation. No significant inhibition of the human ether-a-go-go-related gene potassium channel current was observed in vitro. In a standard battery of in vivo safety pharmacology studies, no adverse events (AEs) of ATI-450 were found on the respiratory and central nervous systems following single dose oral administration up to 45 mg/kg in rat. In a cardiovascular study in mini-pig, no ATI-450-related changes in electrocardiogram (ECG) waveform (PR interval, QRS interval, and corrected QT interval [QTcB]) were observed; however, ATI-450 administration at a dose level of 45 mg/kg was associated with a decrease in arterial blood pressure approximately 2 through 6 hours post-dose, and an elevated heart rate and body temperature

approximately 7 through 18 hours post-dose. Arterial blood pressure returned to baseline by 8 hours post-dose, with heart rate and body temperature returning to baseline by 24 hours post-dose. No effects were noted in animals given 5 or 15 mg/kg.

ATI-450 was not genotoxic in the bacterial reverse mutagenicity assay or in the in vitro chromosomal aberration assay using cultured human peripheral blood lymphocytes, or in an in vivo micronucleus assay in the rat.

Thirteen-week oral toxicity studies were conducted in rats and mini-pigs at dose levels of 3, 10, and 30 mg/kg/day and 10, 30, and 60 mg/kg/day, respectively. There were no ATI-450-related adverse effects noted in either species. ATI-450-related findings in rats given oral doses up to 30 mg/kg/day included a mild to moderate myocyte degeneration, which did not have any effect on the health and well-being of the animals and was not observed after a 4-week non-dosing recovery period. There were no adverse effects on clinical pathology (hematology, clinical chemistry, coagulation, urinalysis). In mini-pigs given oral doses up to 60 mg/kg/day, sporadic and transient clinical signs of warm to touch and hypoactivity were observed once or twice during the 13-week dosing period in 1 or 2 animals given 30 or 60 mg/kg/day. As these were isolated incidences, they were not considered to be adverse. No adverse effects of treatment were observed on clinical pathology (hematology, clinical chemistry, coagulation, urinalysis), nor were there any gross post-mortem or histopathologic findings observed in mini-pigs after 13 weeks of daily oral treatment.

Based on the results of the 13-week oral toxicity studies in rats and mini-pigs, the No-Observed-Adverse-Effect Level was considered to be 30 mg/kg/day in rats and 60 mg/kg/day in mini-pigs.

In conclusion, ATI-450 selectively blocks p38α activation of the proinflammatory kinase MK2 while sparing p38α activation of other effectors such as PRAK and ATF2. Through this mechanism, ATI-450 inhibits inflammatory pathways (such as TNF-α and IL-1β), implying it has potential in a broad range of inflammatory indications. By avoiding direct inhibition of p38, which could lead to inhibition of anti-inflammatory substrates of p38, ATI-450 has the potential to avoid transient efficacy associated with global p38 inhibitors.

1.1.4.4 CLINICAL STUDIES

A single and multiple dose ascending study of ATI-450 in healthy volunteers has been conducted: ATI-450-PKPD-101.

ATI-450-PKPD-101 consisted of multiple parts. A total of 32 male and female subjects were enrolled into Part A of the study where 4 ascending single doses (10 mg, 30 mg, 50 mg and 100 mg) were explored. Eight subjects were randomized at each dose level to receive a single oral dose of ATI-450 (n=6) or placebo (n=2). The 100 mg cohort was repeated following a high fat breakfast to explore the fed-fasting PK of ATI-450.

In Part B, 3 ascending multiple doses (10 mg twice daily [BID], 30 mg BID and 50 mg BID) were explored in 30 male and female subjects. Ten subjects were randomized to receive multiple oral doses (6.5 days) of ATI-450 (n=8) or placebo (n=2) at each dose level.

The potential for a PK drug-drug interaction between ATI-450 and methotrexate (MTX) was investigated in healthy male subjects after administration of a single 7.5 mg oral dose of MTX alone or after twice daily oral administration of ATI-450 at 50 mg (n=15).

Data demonstrate that ATI-450 was well tolerated at all doses in the study. No serious adverse events (SAEs) or severe intensity events were reported. The most common AEs (reported by 2 or more subjects who received ATI-450) were dizziness, headache, upper respiratory tract infection, constipation and abdominal pain. All events were

of mild intensity. A trend of a decrease in absolute neutrophil count (ANC) was observed concurrent with dosing of ATI-450 without correlated clinical sequelae. This effect is consistent with the pharmacodynamic profile of certain anti-TNF therapies.[31] No subject had an ANC value <500 cells/µL. Other laboratory findings were generally unremarkable including CBC's, BMP, LFT, LDH and CPK. There were no findings of myocyte degeneration as noted in the pre-clinical rat model.

After single oral doses (10 mg to 100 mg), ATI-450 was rapidly absorbed with median time to maximum plasma concentration (t_{max}) values ranging from 2.0 to 4.0 hours. Systemic exposure to ATI-450 (as measured by mean maximum plasma concentration [C_{max}] and area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$]) increased approximately proportionally with dose between 10 and 100 mg, suggesting that the PKs of ATI-450 are dose-independent (i.e., linear) over the dose range evaluated. Elimination of ATI-450 from plasma was moderately slow, with mean terminal half-life ($t_{1/2}$) values ranging from approximately 9 to 11 hours. After oral administration of ATI-450 at 100 mg with a standardized high fat, high-calorie breakfast, the median t_{max} was delayed (6.0 hours versus 2.0 hours), but there did not appear to be any appreciable impact on systemic exposure to ATI 450 (C_{max} was ~9% lower and $AUC_{0-\infty}$ was ~24% higher in the fed state).

The PK behavior of ATI-450 after multiple dose administration was consistent with that observed following single doses. Trough concentrations of ATI-450 were generally similar on Days 2 through 7, suggesting that the subjects were at or near steady-state by Day 2 of BID administration. Systemic exposure to ATI-450 on Day 7 of dosing was approximately dose-proportional between 10 and 50 mg. A small amount of accumulation (up to 1.4-fold) was observed following multiple dosing, which was not unexpected given the $t_{1/2}$ of ATI-450 and the length of the dosing interval.

The pharmacodynamics (PD) of ATI-450 were explored by investigating the inhibition of cytokines of interest in blood samples collected from subjects in ATI-450-PKPD-101. For 10 mg BID, mean trough drug levels were below the 80% inhibitory concentration (IC80) for IL-1β and TNFα. At 30 mg BID, mean trough drug levels were above the IC80 for IL-1β, but not for TNFα. At 50 mg BID, mean trough drug levels were above the IC80 for IL-1β and TNFα. No dose level achieved mean trough levels above the IC80 for IL-6, but the 50 mg BID dose level produced drug levels that were higher than the IC50 for IL-6 for at least part of the dosing interval.

The safety, PK and PD data support the 50 mg BID dose level as the most appropriate for investigation in this study.

1.2 Rationale

ATI-450 is an oral small molecule MK2 inhibitor that potently inhibits multiple inflammatory cytokines (TNFα, IL1β, IL6 and IL8). It has been established to be well tolerated, with a good PK/PD profile, in Phase 1. ATI-450 is Phase 2 ready.

COVID-19 morbidity and mortality has been associated with Cytokine Release Syndrome (CRS) and Acute Respiratory Distress Syndrome (ARDS). Therapies such as anti-IL6 monoclonal antibodies appear to be effective CRS treatments in the critical care environment, based on their potent inhibition of a single cytokine target. By potently inhibiting multiple cytokines involved in CRS, ATI-450 may offer a viable and effective approach to managing this condition. There is clearly a need to develop additional therapeutic options to reduce morbidity/mortality and meet healthcare resource needs.

We propose that ATI-450 is developed initially as a potential treatment for patients hospitalized with COVID-19 related CRS. We aim to explore if ATI-450 can improve clinical symptoms and signs in such patients, with an

additional aim of reducing healthcare utilization by preventing progression to mechanical ventilation and/or reducing hospital occupancy.

1.3 Risk/Benefit Assessment

1.3.1 KNOWN POTENTIAL RISKS

Immediate Risks	Acute neutropenia Upper respiratory infection Headache, dizziness
Long-range Risks	Unknown
Other Risks	Possible bacterial and fungal infection

1.3.2 KNOWN POTENTIAL BENEFITS

Immediate Potential Benefits	Improvement of clinical symptoms due to COVID (fever, oxygenation) Reduction in ICU ventilation Reduction in ARDS
Long-Range Potential Benefits	Reduce healthcare utilization by preventing clinical progression due to COVID

1.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Cytokine release syndrome and elevated neutrophil counts has been associated with ARDS and the severe complications and death associated with COVID-19 infection. The investigational drug, ATI-450, can reduce many of these inflammatory cytokines and has been associated with reduction in neutrophil counts in a Phase I study. In patients with moderate to severe COVID-19, the benefit of attempting to reduce cytokine release outweighs the risk of this study drug.

Therefore, the potential benefit of this study is judged to outweigh risk and the risk/benefit ratio is in favor of benefit.

1.4 Measures to Minimize Bias: Randomization and Blinding

This study is randomized and double-blinded to reduce or avoid bias. A randomization schedule will be generated by an independent unblinded statistician prior to the start of the study. Furthermore, consecutive participants will be randomized according to the randomization schedule to further avoid bias.

2 HYPOTHESIS

We hypothesize that MK2 pathway blockade during active COVID-19 infection in hospitalized patients will result in improvement in respiratory-failure free survival.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVES

3.1.1 Primary Objectives

To assess the efficacy of ATI-450 on hypoxic respiratory failure-free survival in patients with moderate-severe COVID-19

3.1.2 Secondary Objectives

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

To assess the safety of ATI-450 in patients with moderate-severe COVID-19.

To assess the anti-inflammatory and immune effect of ATI-450

3.2 ENDPOINTS

To assess the pharmacodynamics of ATI-450 in patients with moderate-severe COVID-19 (based on changes in cytokine and biomarkers)

3.2.1 PRIMARY ENDPOINT

What is being measured	Measurement time frame	Measurement Tool
Proportion of responders on Day 14 defined as all subjects who are alive, free of respiratory failure (do not require supplemental oxygen) and do not experience negative intercurrent events by Day 14 of the trial will be considered responders. [1]	Study Day 14	Noted in patient medical record or Day 14 Follow-up call

[1] Patients with pre-existing oxygen requirements who return to at least their baseline pre-COVID-19 infection oxygenation level will be considered to have successfully achieved the respiratory-free failure survival endpoint.

3.2.2 Secondary Endpoints

What is being measured	Measurement time frame	Measurement Tool
Change in 7 point-ordinal scale	Baseline, Day 3, Day 7, Day 14, Day 28 and follow-up.	Using WHO COVID-19 Ordinal scale measuring: Proportion and time to patients with greater than 2 point improvement on the 7 point categorical scale

Change in oxygen saturation-normalization	Baseline and continuous throughout hospitalization	Peripheral capillary pulse oximeter to measure: SpO2/FiO2 ratio over time, sustainment of normalization in 24 hours, and relative shifts in SpO2/FiO2 categories (<235, between 235 and 315, greater than 315) over time
Need for advanced respiratory care	Baseline and continuous throughout hospitalization	Derived from medical record: time of intubation in the ICU, duration of ICU care in days, duration of overall hospitalization in days
All-cause mortality	Baseline and through d60	Noted in patient medical record
Number and percent of adverse events (AEs) and serious adverse events (SAEs); mean change from baseline lab values, vital signs, and ECG	Baseline through day 14 or at discharge <d14, at d28 ±3, d45 ±3 and d60 ±3 (lab values will be examined up to d45)[2]	CTCAE v5.0; changes in CBC, CMP, Mg, PT/INR, PTT, GGT, hsCRP, D-dimer, LDH, ferritin, creatine kinase, troponin-i, pro-calcitonin; standard vital signs measurement with pulse ox; ECG
Proportion of participants with normalization of fever for 24h	Baseline through day 14 or at discharge <d14	Standard daily vital measurement and obtained from patient medical record
Development of new bacterial or fungal infection (AE of Special Interest)	Continuous throughout hospitalization	Noted in patient medical record
Incidence of ARDS[3] through day 14 or at discharge <d14	From day 1 though day 14 or at discharge <d14	Noted in patient medical record
Change in plasma cytokines IL-1β, IL-6, IL-8 and TNF-α	Baseline, day 3, day 7 (or discharge <d7), day 14 (or discharge >d7 and <d14)	Plasma collected from blood and assayed on Luminex panel performed by KUMC BBV Core

[2] For clarification, lab values will be collected at baseline, day 3, day 7 (or discharge <d7), day 14 (or discharge >d7 and <d14), at day 28 ±3, day 45 ±3. Vital signs, pulse ox will be collected baseline through day 14 or at discharge <d14, at d28 ±3, d45 ±3 and d60 ±3 (lab values will be examined up to d45)

[3] ARDS Criteria:

- PaO2/FiO2 ≤ 300 (adjusted for barometric pressure).
- Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph.
- Requirement for positive pressure ventilation via endotracheal tube.
- No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure ≤ 18 mmHg.

3.2.3 Exploratory Endpoints

The following endpoints may be assessed.

What is being measured	**Measurement time frame**	**Measurement Tool**
Change from baseline in proportion lymphocytes and myeloid cells	Baseline, day 7 (or discharge <d7), day 14 (or discharge >d7 and <d14), d28	Buffy coat collected from whole blood and assayed by Gan lab and KUMC Flow Cytometry Core

Change in plasma cytokines GM-CSF, sIL-2R, IFNγ, IL-17, IL-18, IL-10, IL-1α, IL-1RA, G-CSF, MIP1a, and MCP1, IP10, TGFβ1	Baseline, day 3, day 7 (or discharge <d7), day 14 (or discharge >d7 and <d14), d28	Plasma collected from blood and assayed on Luminex or MSD panel performed by KUMC BBV Core
Change in SARS CoV-2 virus detection by RT-PCR from nasopharynx testing or by antibody testing from saliva	By RT-PCR testing: Baseline, day 14 or at discharge <d14, day 28 By Saliva antibody testing: Baseline, day 14 or at discharge <d14, and day 28	PCR and saliva testing at KUMC clinical labs or affiliates
Molecular studies on PBMCs and neutrophils	Baseline, day 7 (or discharge <d7), day 14 (or discharge >d7 and <d14), day28	RNA, protein, ex-vivo assays
Evaluation of renal function from baseline	Baseline, day 3, day 7 (or discharge <d7), day 14 (or discharge >d7 and <d14), d28	Evaluating normal renal function, renal injury markers, urine output, urinalysis

4 STUDY DESIGN

4.1 Overall Design

This 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 severe COVID-19 disease.

Overall Hypothesis
We hypothesize that MK2 pathway blockade during active COVID-19 infection in hospitalized patients will result in improvement of oxygen saturation.

4.2 Justification for Dose

ATI-450: 50 mg twice daily has shown tolerability and safety in a Phase I clinical study and biochemical correlates demonstrate an ability to substantially reduce inflammatory cytokines IL-1β, IL-6, IL-8, and TNFα

4.3 End of Study Definition

Completion of single cycle of treatment with 14 day follow or stopped due to participant factor or physician discretion.

4.4 Standard of Care

Standard of care will be provided to manage vital signs and oxygenation. We recognize that the standard of care for COVID-19 continues to evolve. Should medications or treatments that are listed in Section 10.4.1.3 become a new standard of care per FDA approval or is FDA approved for use as emergency use only, this will supersede the

prohibited medication list specified in Section 10.4.1.3. Patients taking these newly approved medications may be in the placebo or active treatment arm. We recognize that changes in standard of care over time and potentially with other enrolling institutions (should we open as a multi-center study) may provide confounding results. This will be taken into consideration when performing our final analysis.

Furthermore, we recognize during this pandemic that different hospitals and facilities will have varying access to care based on resources, personnel, expertise, availability of drug and/or respiratory equipment, et al., in addition to the “peak” of infections that maybe occurring at certain times.

5 PARTICIPANT SELECTION

Patients with moderate-severe SARS-CoV-2 viral infection may be eligible for this trial if they meet all entry criteria.

5.1 Inclusion Criteria

PARTICIPANT MRN		**PARTICIPANT INITIALS**
Verified	**Criteria**	
	5.1.1	Able to comprehend and be willing to sign the Institutional Review Board (IRB)-approved subject informed consent form (ICF) prior to administration of any study-related procedures, or consent from surrogate decision maker when the above criteria cannot be met
	5.1.2	Male or non-pregnant female adult ≥18 years of age at time of enrollment; female patients must have a negative serum pregnancy test at study enrollment
	5.1.3	Has laboratory-confirmed COVID-19 coronavirus infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in nasopharyngeal testing within 14d of enrollment.
	5.1.4	Hospitalized as a result of symptoms and signs related to COVID-19 infection, and ≤14 days since positive test
	5.1.5	Evidence of hypoxic respiratory failure: SpO2 ≤93% on room air or supplemental oxygen, or SpO2 >93% requiring ≥ 2L O2, or Pa02/Fi02 ratio <300mmHg, or tachypnea (respiratory rate ≥ 30 breaths/min) and Evidence of pulmonary involvement by chest imaging or pulmonary exam
Adequate organ function, defined as follows:		
	5.1.6	Absolute Neutrophil Count ≥1.5K/UL
	5.1.7	White blood cell (WBC) count ≥3.0×103 cells/mm3
	5.1.18	Platelets ≥ 100K/UL
	5.1.9	Hemoglobin ≥10 g/dL
	5.1.10	Serum creatinine clearance > 50 mL/min
	5.1.11	Total bilirubin ≤ 2.0 x ULN
	5.1.12	Aspartate aminotransferase and alanine aminotransferase < 2.0 x ULN
	5.1.13	Females of child-bearing potential and males with partners of child-bearing potential must agree to practice sexual abstinence or to use the forms of contraception listed in Child-Bearing Potential/Pregnancy section for the duration of study participation and for **30 Days for females and 90 days for males** following completion of therapy.

5.2 Exclusion Criteria

Participants meeting any of the exclusion criteria listed below at screening will be excluded from study participation.

PARTICIPANT MRN	**PARTICIPANT INITIALS**

No	Criteria	
	5.2.1	Known hypersensitivity to ATI-450
	5.2.2	History or evidence of active or latent tuberculosis or recent exposure (within last 30d) to a person with active Tb
	5.2.3	Evidence of active, untreated bacterial or fungal infection. Patients who are treated with antibiotics or anti-fungal medication for active infection must complete the treatment course before being eligible. Use of antibiotic or anti-fungal medication as standard care in the absence of objective evidence (i.e. culture data) of infection are allowed.
	5.2.4	Active use of immunosuppressant medication(s) (i.e. anti-rejection, immunomodulators or immunosuppressant drugs, including but not limited to IL-6 inhibitors, TNF inhibitors, anti-IL-1 agents and JAK inhibitors within 5 half-lives or 30 days (whichever is longer) prior to randomization. Previous use of hydroxychloroquine or chloroquine is allowed in this study. Previous or current use of dexamethasone is allowed in this study.Use of hydroxychloroquine/chloroquine will be discontinued at randomization.
	5.2.5	Cancer patients undergoing active oncologic treatment. Patients who have completed therapy and are deemed in remission or no evidence of disease may be enrolled.
	5.2.6	Active participation in a concurrent COVID-19 clinical trial with investigative medical drug or therapy (see Section 10.4.2). However, co-enrollment for non-investigative drug or therapy (e.g. proning) will be allowed; use or repurposing of FDA approved treatments will be considered at the discretion of the medical monitor.
	5.2.7	In the opinion of the investigator, unlikely to survive for at least 48 hours from screening or anticipate mechanical ventilation within 48 hours
	5.2.8	Pregnancy or breast feeding
	5.2.9	Prisoner
	5.2.10	Intubation and ventilation at time of enrollment
	5.2.11	Known history for HIV, hepatitis B or C infection. Patients with serologic evidence of hepatitis B vaccination (hepatitis B surface antibody without the presence of hepatitis B surface antigen) will be allowed to participate.
	5.2.12	History of a past or current medical condition that in the opinion of the treating physician would compromise patient safety (e.g. uncontrolled HIV) by participation in the study.

6 CHILD-BEARING POTENTIAL / PREGNANCY

Because the effect of the study drug is considered possibly teratogenic and has potential risks to the fetus, pregnant females will not be included in the study. However, no female of childbearing potential will be excluded from the study.

An effective form of contraception of the woman's choice will be required during study participation. Female participants should not get pregnant or breastfeed for **30 days** after last dose of study medication.

Male participants should not donate sperm or father a child while participating in this study and for **90 days** after the last dose of the study medication.

Women of childbearing potential and male participants must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. If a woman becomes pregnant or suspects she is pregnant while participating in this study or if her male partner is a participant in this study, the treating physician should be informed immediately.

A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy;

or

- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)

Acceptable forms of birth control are listed below and must be documented in the participant's chart:

- Sexual Abstinence

OR

- One Barrier method (cervical cap with spermicide plus male condom; diaphragm with spermicide plus male condom)

PLUS

- Hormonal method (oral contraceptives, implants, or injections) or an intrauterine device (e.g., Copper-T).
- If a woman becomes pregnant or suspects she is pregnant (missed or late menstrual period) while participating in this study, she should inform her treating physician immediately.

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she should inform her treating physician immediately.

If the partner of a man becomes pregnant or suspects she is pregnant while he is participating in this study, he should inform his treating physician immediately.

Men of child-bearing potential must not father a child or donate sperm while receiving investigational product and for **90 days** after their last study treatment.

6.1 Screen Failures

Patients who fail screening can be re-screened at a later date. Patients who have an active bacterial or fungal infection who have initiated and been on anti-microbial therapy for at least 3 consecutive days (72 hours) may be eligible for repeat screening as long as they meet eligibility criteria. Oncology patients will also be eligible for rescreening if meeting the above eligibility criteria. Patients who discontinue active chemotherapy, targeted therapy or bio-immunotherapy or have been off treatment for over a day with an ANC ≥1500 mmc are eligible for rescreening.

Screen failures will be offered standard of care treatment per institutional guidelines and physician discretion. They will not be counted towards enrollment and will not be included in analysis of the data.

6.2 Participant Replacement

Participants will not be replaced once treated.

7 PARTICIPANT REGISTRATION PROCEDURES

7.1 General Guidelines

Eligible participants will be registered, and registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before initiating treatment will be considered ineligible and study treatment will be denied.

Issues that would cause treatment delays should be discussed with the Sponsor/Investigator. If a participant does not receive protocol therapy following registration, notify both Drs Gregory Gan and Deepika Polineni and update participant's status in the CRIS (Velos) system.

8 PHARMACEUTICAL INFORMATION

8.1 ATI-450

8.1.1 Overview – Prescribing Information

Test Product	
Substance:	ATI-450
Strength:	50 mg
Dosing frequency	Twice daily
Mode of administration:	Oral tablets
Manufacturer:	Emerson Resources

8.1.2 Packaging and Labeling Information

ATI-450 will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

ATI-450 will be supplied in high-density polyethylene bottles.

Study medications will be shipped and stored under controlled conditions according to the storage requirements.

Refer to the pharmacy manual for full details for packaging, labeling, and shipment of the study medication.

The funder, Aclaris, or designee will supply the study medications.

8.1.3 Preparation/Mixing Instructions

ATI-450 will be produced as a solid, pre-formulated, rapidly disintegrating tablet. No additional patient preparation or mixing will be necessary for the patient prior to taking it.

8.1.4 Drug Storage and Stability

The investigator (or designee) is responsible for the safe and proper storage of study medication at the site. ATI-450 will be stored under controlled conditions according to the storage requirements described on the label(s). Study medications should be stored at 15°C to 25°C (59°F to 77°F), away from heat moisture and direct light. The investigator (or designee) will instruct the investigational pharmacy to store the study medication in accordance to the instructions on the label(s).

In case of temperature excursion, the investigation team will be notified and noted in patient record. No change or pill replacement are planned.

8.1.5 Pharmacodynamics

The pharmacodynamics (PD) of ATI-450 were explored by investigating the inhibition of cytokines of interest in blood samples collected from subjects in ATI-450-PKPD-101. For 10 mg BID, mean trough drug levels were below the 80% inhibitory concentration (IC80) for IL-1β and TNFα. At 30 mg BID, mean trough drug levels were above the IC80 for IL-1β, but not for TNFα. At 50 mg BID, mean trough drug levels were above the IC80 for IL-1β and TNFα. No dose level achieved mean trough levels above the IC80 for IL-6, but the 50 mg BID dose level produced drug levels that were higher than the IC50 for IL-6 for at least part of the dosing interval.

The safety, PK and PD data support the 50 mg BID dose level as the most appropriate for investigation in this study.

8.1.6 Safety/Toxicology

Pre-clinical:
In vitro, no appreciable off-target interactions were observed in broad profile screening against receptors, enzymes, and transporters relevant for safety evaluation. No significant inhibition of the human ether-a-go-go-related gene potassium channel current was observed in vitro. In a standard battery of in vivo safety pharmacology studies, no adverse events (AEs) of ATI-450 were found on the respiratory and central nervous systems following single dose oral administration up to 45 mg/kg in rat. In a cardiovascular study in mini-pig,

no ATI-450-related changes in electrocardiogram (ECG) waveform (PR interval, QRS interval, and corrected QT interval [QTcB]) were observed; however, ATI-450 administration at a dose level of 45 mg/kg was associated with a decrease in arterial blood pressure approximately 2 through 6 hours post-dose, and an elevated heart rate and body temperature approximately 7 through 18 hours post-dose. Arterial blood pressure returned to baseline by 8 hours post-dose, with heart rate and body temperature returning to baseline by 24 hours post-dose. No effects were noted in animals given 5 or 15 mg/kg.

ATI-450 was not genotoxic in the bacterial reverse mutagenicity assay or in the in vitro chromosomal aberration assay using cultured human peripheral blood lymphocytes, or in an in vivo micronucleus assay in the rat.

Thirteen-week oral toxicity studies were conducted in rats and mini-pigs at dose levels of 3, 10, and 30 mg/kg/day and 10, 30, and 60 mg/kg/day, respectively. There were no ATI-450-related adverse effects noted in either species. ATI-450-related findings in rats given oral doses up to 30 mg/kg/day included a mild to moderate myocyte degeneration, which did not have any effect on the health and well-being of the animals and was not observed after a 4-week non-dosing recovery period. There were no adverse effects on clinical pathology (hematology, clinical chemistry, coagulation, urinalysis). In mini-pigs given oral doses up to 60 mg/kg/day, sporadic and transient clinical signs of warm to touch and hypoactivity were observed once or twice during the 13-week dosing period in 1 or 2 animals given 30 or 60 mg/kg/day. As these were isolated incidences, they were not considered to be adverse. No adverse effects of treatment were observed on clinical pathology (hematology, clinical chemistry, coagulation, urinalysis), nor were there any gross post-mortem or histopathologic findings observed in mini-pigs after 13 weeks of daily oral treatment.

Based on the results of the 13-week oral toxicity studies in rats and mini-pigs, the No-Observed-Adverse-Effect Level was considered to be 30 mg/kg/day in rats and 60 mg/kg/day in mini-pigs.

In conclusion, ATI-450 selectively blocks p38α activation of the proinflammatory kinase MK2 while sparing p38α activation of other effectors such as PRAK and ATF2. Through this mechanism, ATI-450 inhibits inflammatory pathways (such as TNF-α and IL-1β), implying it has potential in a broad range of inflammatory indications. By avoiding direct inhibition of p38, which could lead to inhibition of anti-inflammatory substrates of p38, ATI-450 has the potential to avoid transient efficacy associated with global p38 inhibitors.

Clinical:
A single and multiple dose ascending study of ATI-450 in healthy volunteers has been conducted: ATI-450-PKPD-101.

ATI-450-PKPD-101 consisted of multiple parts. A total of 32 male and female subjects were enrolled into Part A of the study where 4 ascending single doses (10 mg, 30 mg, 50 mg and 100 mg) were explored. Eight subjects were randomized at each dose level to receive a single oral dose of ATI-450 (n=6) or placebo (n=2). The 100 mg cohort was repeated following a high fat breakfast to explore the fed-fasting PK of ATI-450.

In Part B, 3 ascending multiple doses (10 mg twice daily [BID], 30 mg BID and 50 mg BID) were explored in 30 male and female subjects. Ten subjects were randomized to receive multiple oral doses (6.5 days) of ATI-450 (n=8) or placebo (n=2) at each dose level.

The potential for a PK drug-drug interaction between ATI-450 and methotrexate (MTX) was investigated in healthy male subjects after administration of a single 7.5 mg oral dose of MTX alone or after twice daily oral administration of ATI-450 at 50 mg (n=15).

Data demonstrate that ATI-450 was well tolerated at all doses in the study. No serious adverse events (SAEs) or severe intensity events were reported. The most common AEs (reported by 2 or more subjects who received ATI-450) were dizziness, headache, upper respiratory tract infection, constipation and abdominal pain. All events were of mild intensity. A trend of a decrease in absolute neutrophil count (ANC) was observed concurrent with dosing of ATI-450withour correlated clinical sequelae. This effect is consistent with the pharmacodynamic profile of certain anti-TNF therapies.[32] No subject had an ANC value <500 cells/µL. Other laboratory findings were generally unremarkable.

8.1.7 Pharmacokinetics and metabolism

Pre-clinical:
The pharmacokinetics (PK) of ATI-450 was studied in mouse, rat, dog, monkey, and mini-pigs. The single dose intravenous PK in all nonclinical species is characterized by a mono-exponential pattern of elimination with mean half-lives ranging from 0.5 to 3.1 hours. After oral dosing, the mean half-life was observed to be up to 6.33 hours in the monkey. Clearance was low in dog and monkey and high in rat and mouse. Oral bioavailability was high in mouse; moderate in rat, dog, and monkey; and lower in mini-pig.

ATI-450 has the potential to translate the observed pre-clinical efficacy into the clinic based upon its oral drug-like properties. Metabolic stability and PK properties of ATI-450 (e.g., long half-life, low clearance, high oral bioavailability, high volume of distribution) are consistent with oral, 1 to 2 times per day dosing in humans.

Clinical:
After single oral doses (10 mg to 100 mg), ATI-450 was rapidly absorbed with median time to maximum plasma concentration (t_{max}) values ranging from 2.0 to 4.0 hours. Systemic exposure to ATI-450 (as measured by mean maximum plasma concentration [C_{max}] and area under the concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$]) increased approximately proportionally with dose between 10 and 100 mg, suggesting that the PKs of ATI-450 are dose-independent (i.e., linear) over the dose range evaluated. Elimination of ATI-450 from plasma was moderately slow, with mean terminal half-life ($t_{1/2}$) values ranging from approximately 9 to 11 hours. After oral administration of ATI-450 at 100 mg with a standardized high fat, high-calorie breakfast, the median t_{max} was delayed (6.0 hours versus 2.0 hours), but there did not appear to be any appreciable impact on systemic exposure to ATI 450 (C_{max} was ~9% lower and $AUC_{0-\infty}$ was ~24% higher in the fed state).

The PK behavior of ATI-450 after multiple dose administration was consistent with that observed following single doses. Trough concentrations of ATI-450 were generally similar on Days 2 through 7, suggesting that the subjects were at or near steady-state by Day 2 of BID administration. Systemic exposure to ATI-450 on Day 7 of dosing was approximately dose-proportional between 10 and 50 mg. A small amount of accumulation (up to 1.4-fold) was observed following multiple dosing, which was not unexpected given the $t_{1/2}$ of ATI-450 and the length of the dosing interval.

8.1.8 Acquisition and Accountability

The study medication must not be used for any purpose other than that defined in this protocol. All supplies of study drug will be accounted for in accordance with Good Clinical Practice (GCP).

The pharmacist or (designee) should maintain accurate records of all study medication supplies received during the study. These records should include the dates and amounts of study medication that were received

at the site, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study medication and study patients. If errors or damage in the study medication shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the study medication accountability records will be provided by each investigator for inclusion in the trial master file (TMF). The study monitor will periodically check the supplies of study medication held by the investigator or pharmacist to verify accountability of the study medication used.

The investigator (or designee) will explain the correct use of the blinded study medication to each patient and will check that each patient is following the instructions properly. The investigator (or designee) will provide the blinded study medication to the investigational pharmacy which will then be dispensed to the patient twice daily. The patient will self-administer the medication twice daily in this study, according to the procedures described in this study protocol.

A record of the number of tablets of ATI-450 dispensed to and taken by each patient will be maintained and reconciled with study medication and compliance records. The study medication start and stop dates, including dates for study medication delays and/or dose reductions, will also be recorded in the eCRF. After the end of the study, all unused study medication and all medication containers should be destroyed at the study center or returned to the sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the sponsor.

8.2 PLACEBO

8.2.1 Overview – Prescribing Information

Test Product	
Substance:	Placebo
Strength:	0 mg
Dosing frequency	Twice daily
Mode of administration:	Oral tablets
Manufacturer:	Emerson Resources

8.2.2 Packaging and Labeling Information

The placebo will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Placebo will be supplied in high-density polyethylene bottles.

Study medications (placebo) will be shipped and stored under controlled conditions according to the storage requirements.

Refer to the pharmacy manual for full details for packaging, labeling, and shipment of the placebo.

The funder, Aclaris, or designee will supply the placebo medications.

8.2.3 Preparation/Mixing Instructions

Placebo will be produced as a solid, pre-formulated, rapidly disintegrating tablet. No additional patient preparation or mixing will be necessary for the patient prior to taking it.

8.2.4 Drug Storage and Stability

The investigator (or designee) is responsible for the safe and proper storage of the placebo at the site. The placebo will be stored under controlled conditions according to the storage requirements described on the label(s). The placebo should be stored at 15°C to 25°C (59°F to 77°F), away from heat moisture and direct light. The investigator (or designee) will instruct the patients to store the placebo medication in accordance to the instructions on the label(s).

In case of temperature excursion, the investigation team will be notified and noted in patient record. No change or pill replacement are planned.

8.2.5 Acquisition and Accountability

The placebo must not be used for any purpose other than that defined in this protocol. All supplies of placebo will be accounted for in accordance with Good Clinical Practice (GCP).

The pharmacist or (designee) should maintain accurate records of all study placebo supplies received during the study. These records should include the dates and amounts of study placebo that were received at the site, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study medication and study patients. If errors or damage in the study placebo shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the study placebo accountability records will be provided by each investigator for inclusion in the trial master file (TMF). The study monitor will periodically check the supplies of study placebo held by the investigator or pharmacist to verify accountability of the study placebo used.

The investigator (or designee) will explain the correct use of the blinded study placebo to each patient and will check that each patient is following the instructions properly. The investigator (or designee) will provide the blinded study placebo to the investigational pharmacy which will then be dispensed to the patient twice daily. The patient will self-administer the placebo twice daily in this study, according to the procedures described in this study protocol.

A record of the number of tablets of placebo dispensed to and taken by each patient will be maintained and reconciled with study placebo and compliance records. The study placebo start and stop dates, including dates for study placebo delays and/or dose reductions, will also be recorded in the eCRF. After the end of the study, all unused study placebo and all placebo containers should be destroyed at the study center or returned to the sponsor (or designee) for destruction. In either instance, complete documentation will be returned to the sponsor.

9 TREATMENT PLAN

The study drug / placebo will be administered within a 14-day cycle. Treatment will be administered to patients while they are hospitalized and will continue their 14-day course of medication as an inpatient. If the patient is discharged alive before treatment is completed, the patient will discontinue drug / placebo but remain on study.

Reported adverse events and potential risks are described in Adverse Events section.

9.1 Treatment Regimen

9.1.1 Treatment Plan

Drug Treatment Schedule

Pre-medications	None
Dose of ATI-450 or Placebo	1 tablet – placebo or 50 mg (as determined from Phase I study) (100 mg total per day).
Route	Oral tablet
Duration of Administration	Up to 14 days while inpatient or if appropriate for discharge home then drug or placebo will be discontinued on last day of being in the hospital
Schedule	Pill will be taken twice daily preferably spaced 12 ±1 hours apart

9.1.2 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Participants will not have access to the study agent at study closure.

9.1.3 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Participants who experience a grade ≥3 toxicity will be evaluated by the medical monitor and study co-PI's, and the case will be forwarded within 24 hours to the KUMC DSMB team to evaluate whether toxicity is attributable to study drug. The DSMB will recommend whether or not patient should be removed from study treatment. There is no planned dose adjustment. Should the patient develop a fungal or bacterial infection while being treated with ATI-450, then the patient will be evaluated as above but will be taken off drug prior to any decision by the DSMB.

10 STUDY PROCEDURES AND SCHEDULE

10.1 Screening/Enrollment/Baseline

Because this is an acute illness, many of the tests required at screening which are performed as part of standard of care within day -2 thru day 0 prior to signing consent will be allowed in this study. Because additional screening labs may be necessary to assess for eligibility after informed consent is obtained, labs from the time of signing informed consent and prior to randomization will be allowed to further assess eligibility in this study. The total

"screening period" will be 96 hours (day -2 through day of enrollment with an additional 2 days after enrollment so that additional screening labs and tests can be performed and resulted). . All resulted screening labs will be reviewed by the investigator. The most recent available resulted labs will be used by the investigator to ensure I/E criteria are met prior to enrollment/randomization.

The following are study procedures. Daily monitoring and care will occur as standard practice.

NOTE: This trial will consist of only one 14 day treatment cycle

Day -2 up to screening day 2

- Informed Consent
- Eligibility review
- COVID-19 and other medical history including time since onset of symptoms and reason for hospital admission
- Demographics - including date of birth, gender, race, ethnicity, and zip code
- Review participant eligibility criteria to ensure participant qualification for study entry
- HIV and Hepatitis history
- Full Physical exam
- Vital signs, weight and height
- Prior and concomitant medications
- Assess for ARDS
- 24 hour COVID-19 PCR testing[§]
- Blood gases (if historic values are available)*
- 12-Lead ECG*[¥]
- CBC with differential*
- CMP*
- C-Reactive Protein*
- Ferritin*
- D-dimer*
- LDH*
- Pro-calcitonin*
- Serum pregnancy test*

[§] For subsites, one can forego another COVID-19 PCR test if that test was performed at the same hospital facility within the screening period. Day 14 (or discharge < day 14) and day 28 COVID-19 PCR tests should be performed using the same assay by the same institution as the Day 0 COVID-19 PCR test for pre-post comparison.

*Historic Lab Values can be used if test performed Day -2 through Day 0

[€] INR alone will be acceptable if PT value is not reported

10.1.1 Procedures During Treatment

Hospital Day 1 (Baseline)

- Limited physical exam
- Vital signs and SpO2 and FiO2
- Urine Output

- Adverse event assessment
- Prior and concomitant medications
- Assess for ARDS
- WHO COVID-19 Ordinal Scale
- Drug Accountability
- CBC with differential
- PT, INR[€]
- PTT
- CMP
- Mg
- GGT
- C-Reactive Protein
- Ferritin
- D-dimer
- LDH
- Phosphate
- Troponin-I
- Cystatin C
- Pro-calcitonin
- Creatine Kinase
- Urinalysis [¥]
- Documentation of proning
- Research Blood Draw Tube #1-4 (prior to morning study drug dose): see chart below for site specific requirements
- Research Blood Draw Tube #5 (hour prior to morning study drug dose): see chart below for site specific requirements (KUMC only)
- Research buccal mucosa tissue brushing (DNA collection) (provide patient Appendix C instructions]Research saliva collection
- Research Urine Collection (prior to morning study drug dose): see chart below for site specific requirements[¥]

[¥] Urine collection and ECG before drug administration is preferred. However, tests collected after morning specimen collection and/or after drug administration will be considered acceptable.
[€] INR alone will be acceptable if PT value is not reported

Research Specimen Collection Guide* ◊

Collection Tube	Non KUMC Sites	KUMC Only
Research Tube #1 (red top/no additive)	Serum	Serum
Research Tube #2 (lavender top/EDTA)	Plasma + Buffy Coat	Plasma; PBMC pooled (RNA, protein, immunophenotyping, neutrophil studies)
Research Tube #3 (lavender top/EDTA)	Plasma + Buffy Coat	
Research Tube #4 (lavender top/EDTA)	Plasma	
Research Tube #5 (lavender top/EDTA)	**Not Applicable**	PBMC (rapid prep) (scRNAseq, RNA, protein)
Research Buccal Mucosa Swab	Buccal Swab (DNA, microbiome)	Buccal Swab (DNA, microbiome)
Research Saliva Collection	**Not Applicable**	Saliva collection
Research Urine Collection	Urine Supernatant	Urine Supernatant

*See Specimen Processing Protocol for processing and shipment instructions
◊ If research specimens become hemolyzed, specimens are to be redrawn (pre- or post-dose)

After research labs have been drawn

- Morning and evening (BID) administration of study medication

Hospital DAY 2 –

- **OPTIONAL EKG - for patients previously on hydroxychloroquine discontinued at randomization; 24 hours ± 2 hour after initiation of drug**
- Morning and evening (BID) administration of study medication
- Vital signs and SpO2 and FiO2
- Urine Output
- Adverse event assessment
- Assess for stoppage criteria
- Drug Accountability

Hospital Day 3 (48 hours post initiating study medication)

- Limited physical exam
- Vital Signs and SpO2 and FiO2
- Urine Output

- Adverse event assessment
- Assess for stoppage criteria
- Concomitant medications
- Assess for ARDS
- Drug Accountability
- WHO COVID-19 Ordinal Scale
- CBC with differential
- PT, INR
- PTT
- CMP
- Mg
- GGT
- C-Reactive Protein
- Ferritin
- D-dimer
- LDH
- Phosphate
- Troponin-I
- Cystatin C
- Creatine Kinase
- 12 Lead ECG[¥]
- Documentation of proning
- Research Blood Draw Tube #1-4 (prior to morning study drug dose): see chart above for site specific requirements
- Research Blood Draw Tube #5 (prior to morning study drug dose): see chart above for site specific requirements (KUMC only)

After all research have been drawn

- Morning and evening (BID) administration of study medication

Hospital Day 4-6

- Morning and evening (BID) administration of study medication
- Assess for stoppage criteria
- Urine Output
- Adverse event assessment
- Assess for ARDS
- Drug Accountability

Hospital Day 7 (or at discharge < day 7)

- Limited physical exam
- Vital signs and SpO2 and FiO2
- Urine Output
- Adverse event assessment
- Assess for stoppage criteria
- Concomitant medications
- Assess for ARDS

- WHO COVID-19 Ordinal Scale
- Drug Accountability
- CBC with differential
- PT, INR
- PTT
- CMP
- Mg
- GGT
- C-Reactive Protein
- Ferritin
- D-dimer
- LDH
- Phosphate
- Troponin-I
- Cystatin C
- Creatine Kinase
- Urinalysis ¥
- Documentation of proning
- Research Blood Draw Tube #1-4 (prior to morning study drug dose): see chart above for site specific requirements
- Research Blood Draw Tube #5 (prior to morning study drug dose): see chart above for site specific requirements (KUMC only)
- Research buccal mucosa tissue brushing (DNA collection) (provide patient Appendix C instructions]
- Research saliva collection
- Research Urine Collection (prior to morning study drug dose): see chart above for site specific requirements ¥

After research labs have been drawn

- Morning and evening (BID) administration of study medication

Hospital Day 8-13

- Morning and evening (BID) administration of study medication
- Assess for stoppage criteria
- Urine Output
- Adverse event assessment
- Assess for ARDS
- Drug Accountability

Day 14 - End of Treatment (discharge < day 14)

- Limited physical exam to include vital signs and SpO2 and FiO2
- Urine Output
- Adverse event assessment
- Prior and concomitant medications
- Assess for ARDS
- WHO COVID-19 Ordinal Scale
- 24 hour COVID-19 PCR testing

- Drug Accountability
- 12 Lead ECG¥
- Survival Status
- CBC with differential
- PT, INR
- PTT
- CMP
- Mg
- GGT
- C-Reactive Protein
- Ferritin
- D-dimer
- LDH
- Phosphate
- Troponin-I
- Cystatin C
- Pro-calcitonin
- Creatine Kinase
- Urinalysis ¥
- Documentation of proning
- Research Blood Draw Tube #1-4 (prior to morning study drug dose): see chart above for site specific requirements
- Research Blood Draw Tube #5 (prior to morning study drug dose): see chart above for site specific requirements (KUMC only)
-
- Research saliva collection
- Research Urine Collection (prior to morning study drug dose): see chart above for site specific requirements ¥

After research labs have been drawn

- Morning and evening (BID) administration of study medication
- Return any and all unused drug to pharmacy for accounting purposes

10.1.2 Post-Treatment Follow-Up Visits

Day 28 Post Hospital Day 1 (±3 days)

- Limited physical exam
- Vital signs and SpO2 and FiO2
- Adverse event assessment
- Prior and concomitant medications
- WHO COVID-19 Ordinal Scale
- 24 hour COVID-19 PCR testing
- Survival Status
- 12 Lead ECG¥
- CBC with differential
- PT, INR

- PTT
- CMP
- Mg
- GGT
- C-Reactive Protein
- Ferritin
- D-dimer
- LDH
- Phosphate
- Troponin-I
- Cystatin C
- Creatine Kinase
- Urine pregnancy
- Urinalysis
- Research Blood Draw Tube #1-4: see chart above for site specific requirements
- Research Blood Draw Tube #5: see chart above for site specific requirements (KUMC only)
- Research buccal mucosa tissue brushing (DNA collection) (provide patient Appendix C instructions]
- Research saliva collection
- Research Urine Collection: see chart above for site specific requirements

Safety Follow up

- **Day 45 Post Hospital Day 1 (±3 days)**
  - Vitals
  - Prior and concomitant medications
  - Follow-up adverse event status
  - Survival Status
  - Pregnancy status
  - CBC with differential
  - PT, INR
  - PTT
  - CMP
  - Mg
  - GGT
  - Creatine kinase
  - Troponin I

- **Day 60 Post Hospital Day 1 (±3 days)**
  - Phone call to follow up adverse event status
  - Survival Status

10.2 Duration of Follow Up

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.

Discontinuation from treatment does not preclude the need to complete follow-up assessments.

10.2.1 Overall Survival Follow Up (OS-FU)

Participants will be followed for survival status until 60 days post hospital day 1 (±3 days) after end of treatment.

Assessment of survival may be completed by phone contact. Death information from public sources, (e.g. death registry, obituary listing, etc.), can also be used when it is available and verifiable.

Patients who are discharged from the hospital to home or another facility (i.e. rehab, SNF) before reaching day 14 of the study in the hospital will be contacted by a study team member by phone in order to collect patient vital status, oxygenation requirements (i.e. on room air, nasal canula, O2 flow rate), assess for any new adverse events or severe adverse events. Patients who cannot (or are unwilling) to return for day 28 or day 45 in-person follow-up visits will be contacted by phone call. Attempts will need to be made to try and collect study specimens and research labs at the appropriate times, if possible. Attempts will also be made to collect any outside records of laboratory data fulfilling study requirements.

10.3 Lost to Follow Up

Institution policy will be followed for participants considered lost to follow up.

10.4 Schedule of Events Table

	Day -2 up to screening day 2[12]	Hospital Day 1[19]	Hospital Day 2[16]	Hospital Day 3[16, 19]	Hospital Days 4-6[16]	Hospital Day 7[16, 19]	Hospital Days 8-13[16]	Day 14 (or D/C)[19]	F/U Day 28[19]	F/U Day 45[19]	F/U Day 60
Informed Consent	X										
Eligibility Review	X	X									
COVID-19, Medical History and Demographics	X										
Prior and Concomitant Medications[10]	X	X		X		X		X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X
Height and Weight[1]	X										
Full Physical Exam[8]	X										
Limited Physical Exam[9]		X		X		X		X	X		
HIV and Hepatitis History	X										
Vital Sign and O2 Usage[2,7,13]	X	X		X		X		X	X	X	
Urine Output Monitor		X	X	X	X	X	X	X			
24-hour COVID-19 PCR test	X							X	X		
12-Lead ECG[17]	X		X[3]	X[14]				X[14]	X		
CBC w/ Diff[6]	X	X		X		X		X	X	X	
PT/INR[6,18]		X		X		X		X	X	X	
PTT[6]		X		X		X		X	X	X	
Complete Metabolic Panel[6]	X	X		X		X		X	X	X	
Magnesium[6]		X		X		X		X	X	X	
GGT[6]		X		X		X		X	X	X	
C-Reactive Protein[6]	X	X		X		X		X	X		
ferritin[6]	X	X		X		X		X	X		
D-dimer[6]	X	X		X		X		X	X		
LDH[6]	X	X		X		X		X	X		
pro-calcitonin[6]	X	X						X			
Phosphate[6]		X				X		X	X		
Creatine Kinase[6]		X		X		X		X	X	X	
Troponin-I[6]		X		X		X		X	X	X	
Cystatin C		X				X		X	X		
Urinalysis[17]		X				X		X	X		

	Day -2 up to screening day 2[12]	Hospital Day 1[19]	Hospital Day 2[16]	Hospital Day 3[16, 19]	Hospital Days 4-6[16]	Hospital Day 7[16, 19]	Hospital Days 8-13[16]	Day 14 (or D/C)[19]	F/U Day 28[19]	F/U Day 45[19]	F/U Day 60
Serum Pregnancy Test	X										
Urine Pregnancy Test									X		
Drug Dosing		X	X	X	X	X	X	X			
Drug Accountability[5]		X	X	X	X	X	X	X			
Research Blood		X[14]		X[14]		X[14]		X[14]	X		
Research Urine Collection[4,17]		X				X		X			
Research Buccal mucosa tissue brushing[4,11]		X[14]				X[14]			X		
Research saliva collection		X[14]				X		X[14]	X		
ARDS Assessment	X	X	X	X	X	X	X	X			
WHO COVID-19 Ordinal Scale		X		X		X		X	X		
Stoppage Criteria Assessment			X	X	X	X	X				
Pregnancy status										X	X
Survival status								X	X	X	X

[1] Most recent value recorded in EMR

[2] Recorded daily vital signs through hospitalization course (baseline thru day of discharge or Day 28). Record vital signs from 00:00 – 24:00 each Day. Vital signs to include: highest and lowest heart rate, highest and lowest respiratory rate, highest and lowest temperature, Highest SpO2 and FiO2 concurrent to highest SpO2, Lowest SpO2 and FiO2 concurrent to lowest SpO2, weight (if available), BP with highest systolic value, and BP with lowest systolic value.

[3] For patients previously on hydroxychloroquine discontinued at randomization; 24 hours ± 2 hour after initiation of drug

[4] Research lab tubes to be collected per respective site instructions (see table page **32**).

[5] record daily while in the hospital drug accountability

[6] SOC lab values will be collected daily throughout hospitalization course (baseline thru day of discharge or Day 28 if available)

[7] SOC arterial blood gas values will be collected if available

[8] Investigator to assess general appearance; head; neck; thyroid; eyes, ears, nose and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; neurological; other, specify.

[9] Investigator to assess changes from baseline in general appearance; head; neck; thyroid; eyes, ears, nose and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; neurological; other, specify.

[10] Prior and Concurrent meds will be recorded as far back as -30 days pre-enrollment

[11] Provide Appendix C patient self-directed instructions on how to perform buccal mucosa swabs

[12] Historic Lab Values can be used if test performed Day -2 through Day 0

[13] Collect Highest O2 Supplementation of the day, options include, Room Air, Nasal Cannula or High Flow Nasal Cannula, Mask or Non-rebreather Mask, Heated High Flow (Comfort Flow), BiPAP or CPAP (excluding chronic CPAP use for sleep apnea), Invasive ventilation, ECMO, or Other (specify other). Also document Highest Oxygen Requiments (L/min), FiO2 concurrent to highest O2 requirement, Lowest Oxygen Requirements (L/min), FiO2 concurrent to lowest O2 requirements, and if patient is in ICU

[14] Prior to morning study drug dose

[15] It is possible that participant's date of discharge will change after Day of Discharge Assessments are performed. If this occurs, do NOT recollect research blood and urine, research buccal mucosa tissue brushing, research saliva, 24-hour COVID-19 PCR test, Phosphate, Cystatin C, and Urinalysis.

[16] If patient is discharged prior to Day 14, follow the schedule of event for Day 14 (EOT). If the patient is discharged before or on Day 7, also collect research buccal mucosa tissue at the EOT visit.

[17] Urine collection and ECG before drug administration is preferred. However, samples collected after morning specimen collection and/or after drug administration will be considered acceptable.

[18] INR alone will be acceptable if PT value is not reported

[19] If research specimens become hemolyzed, specimens are to be redrawn (pre- or post-dose)

10.4.1 Concomitant Medication and Supportive Care Guidelines

10.4.1.1 REQUIRED CONCOMITANT THERAPY

There is no required concomitant medication for this study.

10.4.1.2 RECOMMENDED CONCOMITANT THERAPY

There is no recommended concomitant therapy for this study.

Standard of care will be delivered for patients suffering from respiratory distress or compromise due to moderate to severe COVID-19 infection per the treating physician(s) and/or institutional guidelines; in accordance with evolving CDC guidelines, local-state healthcare recommendations, availability of healthcare resources and FDA approvals and emergency use only approvals. Please refer to section 4.

10.4.1.3 PROHIBITED OR RESTRICTED CONCOMITANT MEDICATIONS

Anti-cytokine based therapy (e.g. Tocilizumab or anti-IL-6 therapy)
Convalescent plasma therapy recovered from COVID-19 patients*
Immunomodulatory therapy (e.g. Remicade, Sulfasalazine)
Oncologic therapy (e.g. chemotherapy, biotherapy)
Oncologic Immunotherapy (e.g. anti-PD-L1, anti-PD-1, anti-CTLA-4)
Hydroxychloroquine/chloroquine will be stopped at randomization
Anti-viral therapy (Remdesivir would not be prohibited)

*Due to FDA EUA for COVID-19 convalescent plasma (CCP), patients receiving CCP will be eligible for this study. It is strongly preferred that participants will have received CCP prior to first dosing of ATI-450/placebo.

10.4.2 VACCINES

The inactivated seasonal influenza vaccine can be given to participants while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor/Investigator and may require a study drug washout period prior to and after administration of the vaccine.

Patients cannot enroll in a concurrent COVID-19 vaccination clinical trial while in this 60 day study period. However, patients enrolled in a COVID-19 vaccination trial that become hospitalized with worsening hypoxic respiratory distress will be eligible for the ATI-450 clinical study provided they meet all other inclusion-exclusion criteria and will participate in both studies.

10.4.3 DIET

Participants should maintain a normal diet unless modifications are required to manage adverse events such as diarrhea, nausea or vomiting, or intubation.

11 DOSING DELAYS/DOSE MODIFICATIONS

11.1 Dose Reduction Steps for ATI-450

No planned dosing reductions.

11.2 Dose Modification Guidelines

A patient experiencing a SAE will be evaluated for whether this is attributable to the drug or due to the patient's disease progression course in order to determine whether the patient should remain on study treatment.

Dose modifications are not permitted in this study.

11.3 Treatment Duration

Participants will receive treatment until there is unacceptable toxicity or the participant or treating physician determines it is not in the participant's best interest to continue.

There will be no additional medication provided to participants once the 14 day cycle has been completed.

11.3.1 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Participants will not have access to the study agent at study closure.

11.4 Participant Discontinuation/Withdrawal from the Study

- Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Any one of the listed items below will be defined as a stopping criteria event. Participants will be removed from protocol therapy for any of the unacceptable adverse event listed below. Participants will have study treatment withdrawn but will remain in the study for follow-up, if any of the following occur:
- Intubation and ventilation
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s) defined as:
    - Malignancy (except for non-melanoma skin cancers)
    - Hepatitis B re-activation
    - Rhabdomyolysis
    - Demyelinating disease
    - Heart failure
    - Lupus-like syndrome

- Hypersensitivity reaction
- Gastrointestinal perforation
- WBC <1x10^3/μl
- ANC <0.5x10^3/μl
- Platelet count <50x10^3/μl
- Hemoglobin: <6.5 g/dl
- AST, ALT:
  - >5xULN
  - >3×ULN and (total bilirubin >2×ULN or international normalized ratio [INR] >1.5)
  - >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- Serum creatinine: >2×ULN
- Serious bacterial or fungal infection
- Other major developing illness or conditions at the discretion of the treating physician

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Major violation of the study protocol (i.e., unable to adhere to study schedule) that in the opinion of the treating investigator, puts the participant at undue risk
- Discontinuation of the study by KUMC
- Confirmed pregnancy
- Completed Overall Survival (OS) follow up as per protocol
- Lost to follow-up
- Death

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the electronic case report form (eCRF). Alternative care options will be discussed with the participant. Safety monitoring and follow-up assessments should continue as appropriate according to the study schedule, unless the participant has withdrawn consent for study participation. Development of bacterial or fungal sepsis, agranulocytosis, hypersensitivity reaction, et al., will be followed until resolution or stabilization of the adverse event.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in CRIS. In the event of unusual or life-threatening complications, treating investigators must immediately notify the Sponsor/Investigator.

12 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

Although pregnancy is not always serious by regulatory definition, for the purposes of this protocol, this event is considered to be an SAE and follow the SAE reporting timeline.

Refer to Appendix A for additional Adverse Event/Serious Adverse Event information.

12.1 Adverse Event Monitoring

Medical history adverse events are recorded and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Serious adverse event and adverse event monitoring begins after initiation of study treatment and continues until the Day 60 safety follow-up. This Day 60 follow-up check and will be done by phone.

12.2 Adverse Event Reporting

Information for adverse events, whether reported by the participant, directly observed or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the CRIS system within 5 days of being reported.

All adverse events experienced by participants will be collected. Medical conditions are collected as baseline adverse events and evaluated as above. Additional adverse event monitoring begins after initiation of study treatment and continues until the 60 day safety follow up.

Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond the 60 day safety follow up will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the Sponsor/Investigator.

Study participants should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

12.3 Serious Adverse Event Reporting

SAEs, and follow-up information regarding SAEs, regardless of expectedness or relationship will be reported within 24 hours of notification as follows:

- Enter into CRIS (Velos) system
- Submit a complete FDA 3500A MedWatch form and all supporting documents to both KUCC Regulatory department: *KUCC-CTO-IIT@kumc.edu*
- and
- *clinicalsafety@propharmagroup.com (or by fax to 866-681-1063)*.

Follow-up source documentation is required within 5 days.

Local policy will be followed for reporting SAEs to the IRB.

12.3.1 Pregnancy Reporting

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within **30 Days** after the last dose, she must inform the investigator immediately and permanently discontinue study drug. Reporting requirements are the same as for an SAE in above. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male participant becomes pregnant during the male participants participation, or within **90 Days** of his discontinuing treatment in this study, he must inform the investigator immediately. Reporting requirements are the same as for an SAE above. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

12.4 IND Safety Report

The Sponsor will review all IND Safety Reports and ensure they are distributed to the participating institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

All affiliate site INDSR submissions, along with IRB acknowledgement are to be forwarded to The University of Kansas Cancer Center IIT Regulatory Department for placement within the trial master file.

Also, an email or fax reporting on SAEs should be sent to *clinicalsafety@propharmagroup.com (or by fax to 866-681-1063).*

13 MEASUREMENT OF EFFECT

Subjects will be followed daily with monitoring for hypoxic respiratory failure.

Change from baseline to time of discharge in lab values for D-dimer, hsCRP, ferritin, LDH, pro-calcitonin.

ATI-450 mediated inflammatory cytokine (IL-1b, IL6, IL-8, TNFa) reduction will be measured from baseline, during drug treatment and at the final safety follow-up visit to assess for reduction in cytokine levels.

14 TRANSLATIONAL AND BIOCHEMICAL SCIENCE

14.1.1 COLLECTION OF SAMPLES

All COVID-19 samples will be collected and processed using an Institutional Biosafety Committee (IBC) approved protocol. On the selected days per the study table, we will obtain up to 4 purple top (EDTA) tubes, 1 red top tube (serum), 1 buccal swabs scrapings, saliva- collection, and 1 urine specimen cup. At KUMC, all research blood and tissue samples obtained on the patient floor will be sent to the Centralized Clinical lab and material will be picked up on ice by University of Kansas Medical Center (KUMC) Biorepository Core Facility (BRCF)-Biobanking and Biomarker Validation (BBV) core facility. All samples

from KUMC main site will attempt to be isolated for plasma, serum, PBMC's, et al., within 1-2 hours after being taken out from the patient.

Samples originating outside of KUMC will be processed according to the provided lab protocol. Samples will be stored in screw cap vials and labelled appropriately. Samples will be snap frozen in liquid nitrogen and then stored at -80°C. Samples will be shipped to the University of Kansas Medical Center Biorepository Core Facility (BRCF)-Biobanking and Biomarker Validation (BBV) core facility and/or to contracted consulting lab(s) on dry ice and kept frozen for long term sample storage. Samples will be shipped as a Category B Biologic substance and follow standard packaging and shipping procedures as regulated by IATA. For samples originating outside of Kansas City area, these samples will be FedEx shipped overnight in batches to KUMC central repository and/or Aclaris and/or contracted laboratory.

Blood samples will be used to generate plasma, serum, PBMC, and neutrophil isolates. From the PBMCs, samples will be processed for immunophenotyping, RNA and protein isolation. The blood sample will be further processed to obtain neutrophils. Buccal mucosa specimens will be processed for DNA. Urine samples will be collected as well.

Unused tissue (e.g. plasma, buffy coat cells) will be stored at -80°C in the BRCF for future analysis up to 3 years after the study has completed. Samples in storage after this time maybe disposed of or maintained for ongoing studies.

14.1.2 CYTOKINE SECONDARY ENDPOINT

At baseline (d1), d3, d7 , d14 or discharge if <d14 and d28, we will collect 1 tube of blood to isolate serum. Blood will be collected on the floors, sent to the clinical lab and transported to the KUMC Biospecimen and Biomarker Validation (BBV) Core in the Biospecimen Repository Core Facility (BRCF) within 2 hour of being drawn (within 4 hours from outside hospital). All work described is approved by the University of Kansas IBC.

Samples will be batch assayed in order to minimize variations between patients sampled on different days. Cytokines to be assayed will include: IL-1β, IL-6, IL-8, TNFα.

Luminex or MSD Assays - Circulating levels of cytokines of interest in serum or plasma will be quantified using multiplexed fluorescent magnetic bead-based immunoassays (Millipore-Sigma) following manufacturer's protocols. Briefly, an overnight bead capture will be performed at 4 °C in black-walled 96-well plates on a plate shaker at the specified dilution of the serum/plasma. Detection and reporter antibodies (streptavidin-conjugated phycoerythrin) will be added on day 2 and incubated at room temperature with shaking. A Bioplex 200 instrument (BioRad) will be used to measure the mean fluorescent intensity (MFI) values for each marker for each test sample and known standards. Standard curves generated using MFI versus concentration data will be used to calculate the cytokine levels in each sample.

14.1.3 EXPLORATORY ENDPOINTS

14.1.3.1 ADDITIONAL INFLAMMATORY CYTOKINE

Blood collected for serum cytokine analysis as described in 14.1.1 will be utilized for inflammatory cytokine analysis using the same Luminex platform operated by the BBV core facility. Additional inflammatory cytokines to be analyzed include: GM-CSF, sIL-2R, IFNγ, IL-17, IL-18, IL-10, IL-1α, IL-1RA, G-CSF, MIP1α, and MCP1, IP10, TGF-β1.

14.1.3.2 IMMUNE PHENOTYPING AND CELL WORK

At baseline (d1), d7, d14 or discharge if <d14 and d28, we will collect 3 tubes of whole blood which will be separated into buffy coat-PBMCs and plasma for immune cell phenotyping analysis. The banked plasma will be used for future exosome analysis, cfDNA analysis or ex-vivo stimulation assays. A 4th tube of blood will be processed by the Polineni lab using a rapid separation technique using Histopaq 1077 which allows for PBMC isolation in under 2 minutes. Transcriptomic analysis, RNA and immunoblot analysis of p38-MK2-HSP27 signaling axis will be analyzed using this technique. Blood will be collected and processed uniformly by the BBV for buffy coat-PBMCs within 2 hour of being drawn. In 10 ml of blood, approximately 10 million PBMC's can be harvested from the buffy coat but the true number will vary based on numerous health factors with this patient population. Total cells numbers will be counted using an automated cell counter with a disposable hemocytometer. Test for Immunophenotyping will follow standard established FACS analysis protocol; RNA and immunoblot will follow standard qRT-PCR and Western blot techniques using previously published methods.

14.1.3.3 NANOSTRING OR EQUIVALENT TRANSCRIPTOMIC ANALYSIS

PBMC's that are rapidly isolated, and neutrophils slated for RNA analysis via Nanostring or equivalent procedure will be lysed in RLT buffer (Qiagen) and stored at -80°C until ready for RNA processing. We will utilize 300 ng of RNA for targeted transcriptomic analysis comparing the placebo to the drug treatment groups at baseline and at day 7. Alternative large-scale transcriptomic analysis procedures will be considered based on cost and efficiency.

14.1.3.4 NEUTROPHIL ISOLATION AND NEUTROPHIL EXTRACELLULAR TRAP

One tube of blood will be used to isolate PBMC's and the pelleted erythrocytes-neutrophils will be further processed to yield neutrophils. These neutrophils will undergo further *ex-vivo* analysis to examine amount of neutrophil extracellular trap formation in the presence or absence of MK2 inhibition. Additional RNA and protein work will be performed on these cells.

14.1.3.5 BUCCAL MUCOSA SAMPLE COLLECTION

Buccal mucosa swab will be taken at baseline and at day 7 and day 28.

The buccal mucosa swab will be performed by the patient, or study personnel (if patient is unable or would prefer),to collect epithelial cell lining and bacteria within the patient's cheeks and gingival gum area. They

will place the swab/cytobrush in the viral transport medium containing vial. This medium will inactivate virus and cells immediately. Tissue will be harvested for future DNA analysis and will temporarily be stored.

14.1.3.6 SALIVA SAMPLE COLLECTION

We will collect saliva into containers at baseline, day 14 (or at discharge less than day 14) and day 28. Collection tubes will be sealed and the external surface of the collection tubes will be wiped down with disinfecting wipes and temporarily stored.

14.1.3.7 URINE SAMPLES

Urine samples will be collected at the pre-specified time points. Samples will be aliquoted into 1 ml volume into a 1.5 ml cryovial tube, frozen and then stored at -80°C freezer in the BRCF. Future analysis will examine urine markers for fibrosis and inflammation.

15 STATISTICAL CONSIDERATIONS

Details of the statistical summaries will be provided in the study-specific statistical analysis plan (SAP). Generally, the objectives for this study will be assessed via point estimates and corresponding confidence intervals.

15.1 Sample Size Justification

Data from 36 patients (18 randomized to ATI-450 and 18 to Placebo) provide enough precision to ensure that the expected asymmetric 70% confidence interval for the difference in the proportion of responders will be no wider than 31 percentage points. This level of precision for the planned 70% confidence interval will facilitate development decisions in accordance with the methods of Frewer et al. The estimate of the expected 70% confidence interval assumed that the placebo response rate would be approximately 50% on Day 14. The 50% response rate assumption was obtained from the proportion of patients that were either not hospitalized or hospitalized but not requiring supplemental oxygen on Day 14 from the study of lopinavir-ritonavir in adults with severe COVID-19 (Cao B., et al. NEJM 2020).

15.2 Study Populations

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 used for the efficacy analyses and summaries. The FAS will be analyzed/summarized as randomized.
- 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.

15.3 Description of Statistical Methods

Efficacy Analyses

Primary Efficacy Analysis

The study is hypothesis generating. The primary assessment of efficacy for this study will be the point estimate and corresponding asymmetric 70% confidence interval for the difference in proportions of responders between 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 70% confidence interval will be derived using a logistic regression model that includes treatment group, baseline age group (<60 versus >=60), and gender as factors.

Secondary Efficacy Analyses

Supportive analyses will be conducted on the secondary efficacy endpoints described in Section 3.5. Categorical variables will be analyzed using a logistic regression like that described for the primary endpoint. In addition to the point estimate and confidence interval for the difference in proportions for categorical endpoints, odds ratios, corresponding confidence intervals and p-values will be provided. For categorical measures that are recorded over time, separate logistic regression analyses will be conducted at each timepoint.

Continuous secondary efficacy endpoints will be analyzed using a mixed model repeated measures MMRM analysis. The MMRM will include factors for treatment, baseline age group, gender, and scheduled timepoint as well as a random effect for patient. Model based means for each treatment group, model based differences between treatment groups will be provided over time as well as their corresponding confidence intervals and relevant p-values.

For time-to-event data, a two-sided stratified log-rank test will be applied. The stratification factor will be baseline age group (<60 versus >= 60). Estimates of the 25^{th}, 75^{th} percentile and the median (50^{th} percentile) will be provided for each treatment group. Kaplan-Meier Curves and corresponding 95% confidence intervals will be provided as well as p-values based on the stratified log-rank test.

Efficacy Summaries

In addition to the efficacy analyses described above, univariate descriptive statistics (number of observations, mean, standard deviation, univariate 95% confidence intervals, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

Safety Summaries

The FAS population will be used for the analysis of safety data (AEs, exposure to study medication, clinical laboratory values, vital signs, and ECG).

AEs will be coded with the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the date of first administration of study medication and before the date of last administration of study medication + 30 days. TEAEs will be presented by system organ class and preferred term in frequency tables. Patients with multiple AEs will be counted only once within each preferred term and system organ class. Key patient information for patients with an AE with an outcome of death, patients with SAEs, and patients with an AE leading to discontinuation of study medication will be listed.

Laboratory data (hematology, serum chemistry, coagulation, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively. Laboratory data outside study specific reference ranges will be listed. Vital signs and ECG parameters will be presented descriptively.

15.4 Interim Analysis

No interim analysis is planned for this study.

15.5 Intercurrent Events and Missing Data

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

- 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 related to the primary endpoint:

- Early discharge due to recovery

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

Missing data and intercurrent event imputation will be treated in a similar manner as the primary endpoint for secondary endpoints of a categorical nature. 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.

15.6 Multiplicity

This is an early pilot study with a single primary endpoint. All secondary endpoints are considered supportive to the primary. The study is hypothesis generating and not intended to support definitive label claims. Therefore, no measures to control for multiplicity will be implemented in the statistical analyses for this study.

15.7 Study Stopping Rules

If 10% or more of the patients evaluated cumulatively every two weeks demonstrate any adverse event of grade 3 or higher that is attributable to the investigational agent and that is not alleviated or controlled by appropriate care or antibiotic therapy within 14 days, will trigger a full review by the data safety

monitoring committee to determine the appropriate course of action. The DSMB may request suspension of the study to allow time for a full committee review or may permit the study to continue after formal review. The DSMB can, however, request a full review at any time in response to an unexpected toxicity regardless of whether the 10% threshold is met.

16 ASSESSMENT OF SAFETY

16.1 Specification Of Safety Parameters

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting and toxicity assessment.

16.1.1 Definition Of Adverse Events (AE)

Adverse Event
An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the and with any route of administration, formulation, or dose, including an overdose.

Expectedness
An adverse event "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to adverse events that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the Particular drug under investigation.

Events not listed in the investigator brochure are considered "unexpected" and those listed are considered "expected."

Serious
An adverse event or is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening
An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

16.1.2 Relationship To Study Agent

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

Attribution
AEs will be assessed as Unrelated, Possibly Related, Probably Related, or Definitely Related. Possible, Probably, or Related AEs will all be considered Related for this protocol. This is the relationship between an adverse event or serious adverse event and the study treatment.

Attribution will be assigned as follows:

Attribution	Definition
Unrelated	There is no reasonable possibility that there is a causal relationship between the study treatment and the AE.
Related	The AE is **possibly related** to the study treatment.

16.2 Reporting Procedures

16.2.1 ADVERSE EVENT REPORTING

Information for adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the study Case Report Form (CRF) as described in the following sections.

ALL adverse events experienced by participants will be monitored/collected/reported as follows:

- Adverse events will be monitored/collected/reported from the start of study treatment, throughout the study, and up to and including day 30 after the last dose of study drug or until the 30 day safety follow up.

- Adverse Events of Special Interest (AESI): Development of new bacterial or fungal infection in this study is an AESI, and should be reported reguardless of severity or seriousness. Reporting should

be completed using the protocol specific AESI Reporting Form and FDA 3500 A MedWatch form and all supporting documents to both KUCC Regulatory department: *KUCC-CTO-IIT@kumc.edu and clinicalsafety@propharmagroup.com (or by fax to 866-681-1063)*. AESI should also be entered in CRIS (Velos) system

- SERIOUS adverse events that meet the definition(s) of a serious adverse event will be monitored/collected/reported from start of study treatment, throughout the study, and up to and including day 30 after the last dose of study drug or until the 30 day safety follow up.

Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the Sponsor-investigator.

Study participants should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases present before starting study treatment are considered adverse events only if they worsen after initiation of study drug.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis.

All SAEs recorded throughout this study will be continued to be monitored until resolution or stabilization.

16.2.2 Recording Adverse Events And Documentation In *Velos*

All AEs and SAEs regardless of causality must be entered in the Velos system. Unexpected and expected adverse events must be entered within 5 days and include:

- New unexpected adverse events
- Worsening baseline conditions
- Clinically significant laboratory findings
- Disease-related signs and symptoms that were not present at baseline
- Any event of findings that the Investigator feels is clinically significant

Documentation must be supported by an entry in the participant's electronic medical record file. A laboratory test abnormality considered clinically significant (requiring medical intervention) should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, expectedness, relationship to investigational product, action taken and outcome.

16.2.3 Serious Adverse Event Reporting

For serious adverse events, the clinical research site will follow local IRB policies and procedures.

All SAEs regardless of causality must be entered into Velos within 24 hours. Entering the event into Velos will send an automatic email to the KUCC Regulatory team and the KUMC DSMB. The PI's will notify Aclaris

Pharmaceutical, Inc, by email (*PV@aclaristx.com*) after the KUCC Regulatory team and DSMB have been notified.

Follow-up source documentation is required within 5 days.

Send all supporting documents with a cover sheet to:

KUMC DSMB
Email: dstevens@kumc.edu

16.2.4 Summary Of Expedited Serious Adverse Event Reporting

	Relationship to Study Drug	IRB	Velos (KU DSMB and PI)	Funder
Unexpected SAE/AESI	Related	Per local IRB reporting policy	24 hrs	24 hrs
Unexpected SAE/AESI	Not-related	Per local IRB reporting policy	24 hrs	24 hrs
Expected SAE/AESI	Related	Per local IRB reporting policy	24 hrs	24 hrs
Expected SAE/AESI	Not-related	Per local IRB reporting policy	24 hrs	24 hrs

16.2.5 SUBMITTING IND SAFETY REPORTS TO FDA

The University of Kansas Cancer Center Regulatory Affairs Department is delegated by the Sponsor-Investigator to report any IND safety report any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor-investigator needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The following reports require expedited reporting.

- unexpected fatal or life-threatening adverse experiences associated with the use of the drug are to be reported by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32©(2)]
- any adverse experience associated with the use of the drug that is both serious and unexpected is to be reported in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]

16.2.6 Reporting Of Pregnancy

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

Monitoring for pregnancies in female patients will continue from the patient's inclusion in the study until the follow-up visit. Male patients will be required to inform the investigator if their partner becomes pregnant during the study. The investigator should inform the sponsor within 24 hours of learning of the pregnancy or partner pregnancy by completing and submitting a pregnancy report form to the sponsor (or designee).

If a patient becomes pregnant, study medication will be permanently discontinued, and she will be withdrawn from the study after completing the assessments planned for the end of study visit (see Table 1). Any pregnant patient and the fetus will be closely followed up throughout the duration of the pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality).

The investigator will ask the patient to provide informed consent to record information on the health of the baby. Generally, follow-up will be required for no longer than 6 to 8 weeks beyond the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

For any male study patient whose partner becomes pregnant, the investigator will attempt to collect pregnancy information on the male patient's partner while the male patient is in this study.

17 REGULATORY REQUIREMENTS AND DATA REPORTING

17.1 Institutional Review Board/Ethics Committee Approval

Before trial initiation this protocol and informed consent form will be submitted for review and approval by the IRB of record for the clinical site. Any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the IRB. In accordance with FDA 21 CFR 56 of the Code of Federal Regulations the Investigator will forward the Sponsor/Investigator a copy of the IRB approval letter for the initial approval, amendments, informed consent and any informed consent updates.

The Investigator will be responsible for providing the Sponsor/Investigator a list of IRB members including profession and affiliation or a United States Department of Health and Human Services General Assurance number and expiration date. If neither of these is available, the IRB Chairperson must submit a statement indicating the members of the board responsible for the review meet the FDA and other appropriate

regulatory requirements. The labeling for all approved trial medications should be submitted to the IRB for information purposes.

Sub-sites will not be activated until the Sponsor/Investigator has received documentation of IRB approval.

17.2 Investigators Protocol Agreement

The Investigator must sign the Protocol Agreement before the study is activated. The original will be forwarded to the Sponsor/Investigator and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed when a protocol amendment is issued.

17.3 Remaining Samples

Any samples remaining after the trial specified analyses is completed will be stored by the Sponsor/Investigator at the University of Kansas Biospecimen Repository Core Facility if the participant consented for use of their remaining samples for future research purposes. This includes the original specimen collected from the participant (blood, nasal cavity-nasopharynx specimens, bronchoalveolar lavage fluid and lung tissue specimens) as well as derivatives created from the original specimen (DNA, RNA, blocks or slides).

If a participant has not consented for their remaining samples to be used for future research purposes remaining samples and derivatives will be destroyed and documented.

17.4 Confidentiality

The Investigator and any other personnel involved in the trial shall not disclose or use for any purposes other than for the performance of this trial any data, records or other information disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the Sponsor/Investigator and shall be disclosed only to the Investigator or other designated trial personnel.

Participant confidentiality will be ensured by using assigned site-specific participant ID numbers throughout the trial.

17.5 Publication

The Sponsor/Investigator holds the primary responsibility for publication.

Data
Aclaris and its co-development collaborator may use the data generated under the Research Agreement for all purposes, subject to Institutions right to unrestricted publishing.

Publication
KUMC Sponsor/Investigator shall publish the results of the approved study, subject to reasonable delay to allow for filing of patent applications on any inventions (as applicable). Sponsor/Investigator will provide Aclaris with the opportunity to review and comment on any publications, prior to submission.

17.6 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the FDA Modernization Act (FDAMA) and the FDA Amendments Act (FDAA) the Sponsor/Investigator of the trial is solely responsible for determining if the trial and results meet the requirement for submission to the Clinical Trials Data Bank, *http://www.clinicaltrials.gov*. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial location and trial site contact information.

17.7 Required Site Documentation

Before the study is initiated ay any site the following documentation must be provided to the Regulatory Department.

- A copy of the official IRB approval letter for protocol and informed consent.
- A copy of the IRB-approved consent form.
- CVs and medical licensure for the Principal Investigator and all Sub-Investigators who will be involved with conduct of the study.
- Appropriately completed and signed Form FDA 1572 with appropriate documentation.
- COP and CLIA Laboratory certification numbers and institution laboratory normal values.
- Executed clinical research contract.

17.8 Data Management

Web-based eCRFs will be used to collect participant data. All eCRFs and resulting data will be developed and maintained in a manner consistent with currently available regulations and guidance pertinent to the use of computerized systems in clinical trials. All users of the eCRF system will be trained prior to the use of the system.

A Risk-Based Monitoring (RBM) approach will be used focusing on critical variables and triggered events and ensuring the eCRF accurately reflects data recorded in source documents.

17.9 Data Monitoring

Data monitoring procedures will be carried out and will be performed on a regular basis to comply with Good Clinical Practice.

The study will be monitored at appropriate intervals, no less than those assigned per risk level designation, to assure compliance to GCP and to assess the data quality and study integrity.

Interim monitoring visits (IMV) will occur at regular intervals following enrollment/registration of the first study participant with the frequency and duration of each visit depending on recruitment status and participant enrollment/registration.

Review of the case report forms, cross-reference with source documents, review of trial related regulatory documents and logs will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the trial is conducted according to protocol design and regulatory requirements.

The monitor will complete a follow-up letter and provide to the Sponsor/Investigator. The letter will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to ensure compliance. The site will be expected to submit any Corrective and Preventative Action Plan (CAPA) in writing to the Sponsor/Investigator. A copy of the monitoring forms, follow up letter and CAPA will be kept in the site monitor's trial file and will be followed up at the next monitoring session.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

18 DSMB OVERSIGHT

The Data Safety and Monitoring Board (DSMB) of the University of Kansas Medical Center will monitor every participant receiving treatment on this protocol for safety, conduct and scientific progress of research protocols, and the validity and integrity of the data for clinical trials. This protocol will adhere to the policies of the currently approved Data and Safety Monitoring Plan which is in accordance with KUMC-IRB policy and guidelines. The committee is led by a senior practicing pulmonologist and consists of KUMC faculty and staff with expertise in pulmonology, critical care, research, and data management. The DSMB has the authority to require amendments, suspend, or terminate any research activities that fall within its jurisdiction, and can institute other appropriate actions as needed to protect participant safety.

The DSMB is an autonomous committee. However, its actions are communicated to other committees engaged in oversight of clinical research at KUMC. The PI is responsible for forwarding all DSMB letters, including those recommending continuation of the study, to the IRB and PRMC. The PI is notified of DSMB recommendations and is expected to alert all collaborating investigators about the DSMB action.

18.1 Serious Adverse Events

Serious adverse events that require expedited reporting will be reviewed by the DSMB Chair or designee who will determine if immediate action is required. If determined to be necessary by the DSMB, all participating sites will be notified of the event and any resulting action within one working day of this determination. In addition, all other active ATI-450 clinical trial sites (not associated with this protocol) will be informed about the INDSR.

NOTE: If expedited SAE report sent to FDA – then ALL sites with ATI-450 studies must be notified.

18.2 Review of Serious Adverse Event Rates

Once every two weeks, serious adverse event rates will be monitored by the DSMB Coordinator. If any study site has had 2 or more of the same treatment-related SAE reported within one month, or more than 6 of the same treatment-related SAE in 3 months, the DSMB will review summaries of SAEs, and discuss events in detail with the PI. The DSMB chair or designee determines whether further action is required. The Sponsor/Investigator, in collaboration with the DSMB Coordinator ensure that collaborating investigators and IRBs for all participating sites are notified of any resulting action.

18.3 Study Safety and Progress

An overall assessment of toxicities as described in the protocol is reviewed at DSMB meetings. This review enables DSMB committee members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

18.4 Quality Assurance Auditing

The study will be audited at appropriate intervals, no less than those assigned per risk level designation, to assure compliance to GCP and Good Documentation Practices (GCP).

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data.

19 DATA HANDLING AND RECORD KEEPING

19.1 Data Collection and Management Responsibilities

Electronic case report forms (eCRFs) will be completed for each participant enrolled and registered on this study. All CRFs will be customized per this study, in order to emphasize completeness and accuracy. The investigatory and trained study staff will enter and edit the data via a secure network with secure identification and password requirements. A complete electronic audit trail will be maintained.

Source documents serve as the evidence of the existence of the participant and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor/Investigator or assigned Clinical Site Manager.

Data captured in the eCRF is to be transcribed from source documents and must be consistent with any discrepancies explained and document. The medical chart and any other clinical worksheets, procedural reports, etc. will be the source documentation of data captured into the study database.

19.2 Protocol Deviations

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. All deviations will be entered into the CRIS system must be reported to the DSMB. All deviations will be reported to the IRB per local reporting policy.

19.3 Study Closure

Upon study closure, the Sponsor/Investigator and/or Institution will be required to certify that all safety reporting obligations were met.

19.4 Study Records Retention

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, participant diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

20 APPENDICES

Appendix A: Reportable Events

Adverse Event (AE) Definition

Adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship to this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom or disease temporally associated with the use of investigation product, whether or not considered related to the investigational product.

Serious Adverse Event (SAE) Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or causes prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect
- Is an important medical event defined as a medical event or multiple medical events that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgement may jeopardize the participant or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug.

Although pregnancy and potential drug-induced liver injury are not always serious by regulatory definition, for the purposes of this protocol, these events are considered to be an SAE and follow the SAE reporting timeline.

Any component of the study endpoints that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis is reported an SAE.)

NOTE: The following hospitalizations are not considered SAE's:

- An Emergency room or other hospital department visit <24 hours that does not result in admission. Unless considered an important medical or life-threatening event)
- Elective surgery planned prior to signing consent.
- Admissions as per protocol for a planned medical/surgical procedure.
- Routine health assessment requiring admission for baseline/trending of health status. (e.g., routine colonoscopy)

- Medical /surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention. (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Unanticipated Problem

An Unanticipated Problem is any incident, experience or outcome involving risk to participants or others in any human participant research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given the research procedures described in the IRB-approved protocol and informed consent document and the characteristics of the population being studied.
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility the incident, experience or outcome may have been caused by the procedures involved in such research).
- Suggests that the research placed participants or others at a greater risk of harm (including physical, psychological, economic or social harm) that was previously known or recognized.

Suspected Adverse Reaction

A Suspected Adverse Reaction (SAR) is any AE for which there is a reasonable possibility that it was caused by the drug.

Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE. Examples of reasonable possibility are:

- A single occurrence of an event that is uncommon and know to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug.
- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Expectedness and Attribution

Both AE's and SAE's are evaluated with regard to expectedness and attribution.

Expectedness

Expected events are those that have previously been identified as resulting from administration of the agent. For the purposes of this study an event is considered expected when it appears in the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

An event is unexpected when it varies in nature, intensity or frequency from information provided in the

Investigator's Brochure, the package inserts or when it is not included in the informed consent document as a potential risk.

Attribution

Attribution is the relationship between an event and the treatment. Attribution is assigned as follows:

- Definite – The event is clearly related to the study treatment
- Unrelated – There is no reasonable possibility that there is a causal relationship between the study medication and the AE

Adverse Event Monitoring

Medical history adverse events are recorded and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Serious adverse event and adverse event monitoring begins after initiation of study treatment and continues until the Day 60 safety follow up.

Adverse event data collection and reporting are a part of every clinical trial and are done to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies using similar agents.

Adverse events should be evaluated to determine

- Start and end dates
- Severity or grade
- Seriousness
- Relationship to study agent
- Action taken (i.e., dose held, dose reduced, medical intervention)
- Outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Participants experiencing an adverse event, regardless of its relationship to study drug will be monitored until:

- Adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline.
- Clinically significant abnormal laboratory values have returned to baseline.
- The treating investigator has determined there is a satisfactory explanation other than the study drug for the changes observed.
- Death

The following laboratory abnormalities should be documented and reported as adverse events.

- Meets the definition of an SAE.
- Requires medical intervention (i.e., dose modification and/or other intervention such as supportive medication administration, supplementation, physical therapy, diet change, fluid administration, transfusion, additional testing, etc.)

Sponsor/Investigator Reporting to FDA

The University of Kansas Medical Center's Sponsor/Investigator as holder of the IND will be responsible for all communication with the FDA. The Sponsor/Investigator will report any adverse event that is serious, unexpected and reasonably related (possible, probable, definite) to the study treatment.

The Sponsor/Investigator must report the following Suspected Adverse Events as outlined below:

Table 11-1

Event	Report To	Time Frame
Unexpected fatal or life-threatening SAR	FDA	As soon as possible but no later than 7 calendar days after the Sponsor/Investigator's initial receipt of the information.
Any event that is both serious and unexpected SAR	FDA and participating investigators	As soon as possible but no later than 15 calendar days after the Sponsor/Investigator's determine the information qualifies for reporting
Any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies regardless if conducted under an IND or if the Sponsor/Investigator it suggests significant risk to humans exposed to the drug	FDA and participating investigators	As soon as possible but no later than 15 calendar days after the Sponsor/Investigator's determine the information qualifies for reporting
Any findings from animal or in vitro testing, regardless if conducted by the Sponsor/Investigator that suggests a significant risk in humans exposed to the drug	FDA and participating investigators	As soon as possible but no later than 15 calendar days after the Sponsor/Investigator's determine the information qualifies for reporting
Any clinically important increase in the rate of a Serious SAR over that listed in the protocol or Instigator Brochure.	FDA and participating investigators	As soon as possible but no later than 15 calendar days after the Sponsor/Investigator's determine the information qualifies for reporting

Expected SAE's and AE's should be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of the Sponsor/Investigator determines an adverse drug experience not initially determined to be reportable are so reportable the Sponsor/Investigator must report such experience as soon as possible but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to the FDA as soon as possible but no later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone 1-800-FDA-1088 or by fax, 1-800-FDA-0178 using Form FDA 3500 (Voluntary Reporting) for non-IND studies and Form 3500A (Mandatory Reporting) for IND studies.

Guidelines for Processing IND Safety Reports

The US Food and Drug Administration (FDA) regulations require Sponsor/Investigators of clinical studies to notify them and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigation agent. The Sponsor/Investigator will review all applicable IND Safety Reports and has the responsibility to forward the IND safety reports to the affiliate institutions. The affiliate institution investigators are to review and report to their IRB in accordance with local IRB policies and will file a copy with their regulatory documents.

APPENDIX B: WHO Ordinal Scale for Clinical Improvement

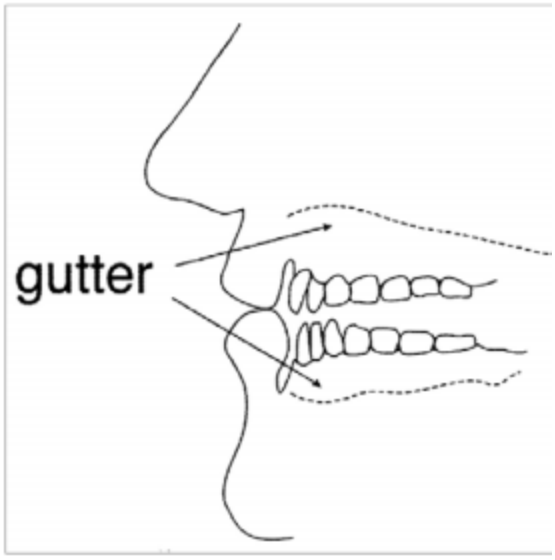
Patient State	Descriptor	Score
Uninfected	No clinical or virologic evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, Mild Disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized, Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation or mechanical ventilation	6
	Ventilation plus additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Appendix C

Buccal Mucosa Swab Protocol for Patients:

This test will be performed on your first and 7th day of the study, both tests being made prior to receiving the study drug. We are collecting two things: 1) cheek-gum cells to look at proteins involved in COVID-19 infection and may predict response to treatment, and 2) cheek-gum cells to look at the DNA to see if there are markers that can predict response to treatment

1. Rinse your mouth prior to performing this procedure (i.e. drinking some water and rinsing it around your mouth is enough)
2. Hold the swab in your hand like you would hold a toothbrush
3. Insert the swab into your month so it is resting between your inner cheek and gum ("the gutter"), close your mouth slightly to keep the brush in place
4. Brush vigorously back and forth with the swab for 15-20 seconds making sure the swab stays as far up in your mouth as possible (i.e. **DO NOT** brush your teeth)
5. After 15-20 seconds, open your mouth and carefully remove swab and move it to the next location in your mouth
6. Repeat steps 2-4 ensuring the upper and lower right gutters and upper and lower left gutters are swabbed using the same swab.
7. When finished, carefully remove the swab from your mouth and place into a new small collection vial.

	1. Please rinse your mouth prior to this procedure 2. Brush and twirl the cytobrush for 15-20 seconds over the following places in your mouth: -the upper and lower left "gutters" -the upper and lower right "gutters" 3. Take the cytobrush, break off the end without touching the brush and deposit this into the fixation solution

LITERATURE REFERENCES

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