A single-center registry and embedded interventional study of the effects of COVID-19 with and without treatment with AT-001 on cardiac structure and function in patients hospitalized for management of COVID-19 infection

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Additional Investigators:	See table below
NYULMC Study Number:	s20-00416
Funding Sponsor:	Applied Therapeutics, Inc. 545 Fifth Avenue, Suite 1400 New York, NY 10017 212.220.9319 www.appliedtherapeutics.com
IND/IDE Number:	IND number 136043 held by Sponsor
Study Product:	AT-001
Study Product Provider:	Applied Therapeutics, Inc. 545 Fifth Avenue, Suite 1400 New York, NY 10017 212.220.9319 www.appliedtherapeutics.com
ClinicalTrials.gov Number	NCT04365699

Protocol Revision History:

Version Number	Version Date	Summary of Revisions Made
1.0	22 MARCH 2020	Initial Draft
1.1	24 MARCH 2020	Updated With AT-001 intervention
1.2	26 MARCH 2020	Revisions to study procedures
1.3	13 APRIL 2020	Addition of NYU Winthrop for AT001 intervention
1.4	03 MAY 2020	Revisions to entry criteria and analysis related to co-enrollment and EUA of remdesivir

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor 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 Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
ARDS	Adult Respiratory Distress Syndrome
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-6	Interleukin-6
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SARS-CoV-2	Severe Adult Respiratory Syndrome Coronavirus2
SOP	Standard Operating Procedure
US	United States

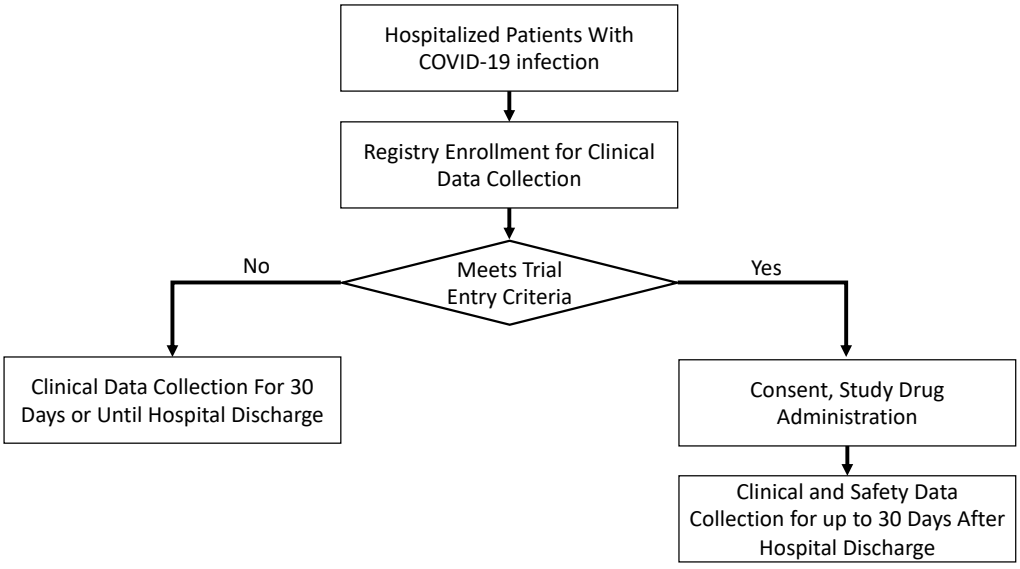
Protocol Summary

Title	*A multi-center registry and embedded interventional study of the effects of COVID-19 with and without treatment with AT-001 on cardiac structure and function in patients hospitalized for management of COVID-19 infection*
Short Title	*Cardiovascular effects of COVID-19*
Brief Summary	*This is a prospective multicenter registry with an embedded open-label randomized clinical trial to determine the effects of standard of care treatment vs. standard of care plus AT-001 on cardiac structure and function and in-hospital survival in patients hospitalized for management of COVID-19 infection. Eligible subjects with COVID-19 infection will be identified at the time of hospital admission based on existing infection control surveillance protocols, and will have clinical data extracted from the electronic medical record to determine clinical characteristics associated with cardiac structure and function and in-hospital survival. A subset of patients with history of diabetes mellitus and/or acute hyperglycemia (any glucose measurement >200 mg/dl) and evidence of acute or chronic heart disease will be treated in an open-label fashion to receive an investigational aldose reductase inhibitor, AT-001 plus standard of care. The primary objective of the interventional study is provide emergency access to open-label treatment to COVID-19 patients with acute cardiopulmonary symptoms.*
Phase	*Phase II*
Objectives	• *To characterize serial measures cardiac structure and function and in-hospital survival in hospitalized patients with COVID-19 infection* • *To develop predictive models of cardiac risk in hospitalized COVID-19 infection patients* • *To assess safety of treatment with AT-001 plus standard of care on in-hospital survival in patients with COVID-19* • *To characterize the effects of treatment with AT-001 plus standard of care on in-hospital mortality, progression of acute lung injury requiring mechanical ventilation, and serial measures of cardiac structure and function*
Methodology	*Prospective, open-label registry with embedded open-label study*

Endpoint	*Primary Endpoint for Registry Study: Proportion of subjects with decreased left ventricular ejection fraction ≥10% from baseline at time of hospitalization* *Primary Endpoint for Embedded Clinical Trial: Safety of AT-001* *Secondary Endpoints (for registry and clinical trial):* • *Change in left ventricular ejection fraction* • *Change in left ventricular end-diastolic diameter* • *Change in left ventricular end-systolic diameter* • *Change in biomarkers of cardiac injury* • *Frequency of atrial fibrillation* • *Frequency of heart block* • *Frequency of non-sustained ventricular tachycardia* • *Frequency of sustained ventricular tachycardia* • *Frequency of ventricular fibrillation* *Secondary Endpoints (for clinical trial):* • *Proportion of subjects requiring mechanical ventilation* • *Proportion of subjects with decrease in left ventricular ejection fraction ≥10% from baseline at time of hospitalization*
Study Duration	*One year*
Participant Duration	*Up to 30 days after hospital discharge*
Duration of IP administration	*1-14 days per treatment physician discretion*
Population	*All subjects hospitalized with COVID-19 infection hospitalized will be enrolled in the registry; a subgroup meeting specific entry criteria listed below will be enrolled in the open-label interventional trial*
Study Sites	*NYU Langone Tisch Hospital (registry and embedded clinical trial)* *NYU Langone Brooklyn Hospital (registry only)* *NYU Langone Winthrop Hospital (registry and embedded clinical trial)* *Bellevue Hospital Center (registry only)*
Number of participants	*500 registry subjects enrolled at all sites* *20 interventional trial subjects at NYU Tisch Hospital and NYU Winthrop*
Description of Study Agent/Procedure	*AT-001 is an investigational novel Aldose Reductase Inhibitor (ARI) in Phase 2/3 development in the US, Canada and Europe for treatment of Diabetic Cardiomyopathy. The US IND# is 136043. A full Investigational Brochure is for the ongoing Diabetic Cardiomyopathy program is attached to this protocol.*
Reference Therapy	*Standard of care*
Key Procedures	*Data extraction from electronic medical record* *Administration of AT-001 1500 mg twice daily for up to 14 days*

Statistical Analysis	***Registry Study*** • *Multivariable logistic regression models and Cox Proportional Hazard models will be used to estimate the association between clinical variables at time of hospital admission and ICU admission with proportion of patients with decreased left ventricular ejection fraction ≥10% and secondary endpoints cardiac structure and function.* • *Multivariable mixed models will be used to estimate the association between serial measures of cardiac structure and function and in-hospital mortality.* ***Interventional Study*** • *Safety assessment of AT-001 based on reported adverse events* • *Exploratory analyses with descriptive statistics to describe clinical outcomes in patients treated with AT-001 plus standard of care*

Schematic of Study Design



1 Key Roles

Name	Role	Appointment	Department	Site
Stuart Katz	Principal Investigator	NYU Grossman SOM	Department of Medicine	NYU Tisch
Judith Hochman	Co-Investigator	NYU Grossman SOM	Department of Medicine	NYU Tisch
Harmony Reynolds	Co-Investigator	NYU Grossman SOM	Department of Medicine	NYU Tisch
Glenn Fishman	Co-Investigator	NYU Grossman SOM	Department of Medicine	NYU Tisch
Alex Reyentovich	Co-Investigator	NYU Grossman SOM	Department of Medicine	NYU Tisch
Claudia Gidea	Co-Investigator	NYU Grossman SOM	Department of Medicine	NYU Tisch
Juan Gaztanaga	Co-Investigator	NYU Grossman SOM	Department of Medicine	NYU Winthrop

2 Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

An outbreak of viral pneumonia in Hubei province China in December 2019 led to the identification of a novel coronavirus (SARS-CoV-2, subsequently renamed as COVID-19) as the etiologic agent.[1, 2] COVID-19 infection rapidly spread through China and then globally to all continents except Antarctica. Based on reported observations from the initial epidemic in China, hypertension and underlying cardiac diseases, as well as diabetes and treatment with immunosuppressants, may be associated with increased risk of death in patients with COVID-19. Like related coronaviruses, COVID-19 infects host cells via interaction with membrane-bound angiotensin converting enzyme-isoform 2 (ACE2) on respiratory epithelium. ACE2 is part of the renin-angiotensin-aldosterone (RAAS) neurohormonal pathway, a neuroendocrine, paracrine, and autocrine system that regulates cardiac structure and function, vasomotor tone, sodium metabolism, and blood pressure homeostasis. COVID-19 infection is also associated with activation of inflammatory cytokines that induce myocardial contractile dysfunction, myocyte cell injury, cardiac arrhythmias, and vascular endothelial cell and smooth cell dysfunction.

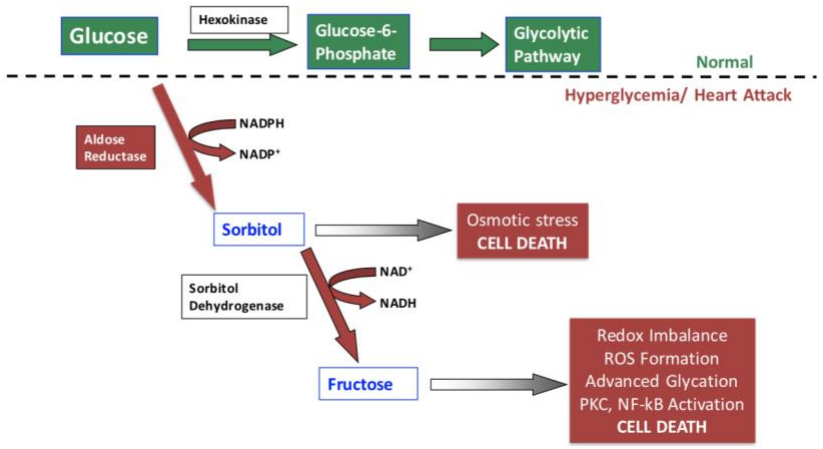
Initial reports from China in 41 patients indicated that severe COVID-19 infection in hospitalized patients is associated with approximately 10-20% risk of cardiac complications include increased biomarkers of myocardial injury, decreased left ventricular contractile function, cardiac arrhythmias, chest pain, hypotension, and fatal circulatory collapse.[3] There are also reported anectodal cases of sudden cardiac arrest occurring in young patients recovering from COVID-19 induced acute respiratory failure.

The current study is being undertaken to create increase knowledge of the cardiovascular complications of COVID-19 infection at NYU Langone Health and Bellevue Hospital Center. A prospective registry is proposed to characterize the cardiovascular manifestations of COVID-19

infection in US patients. The prospective registry also provides a platform for execution of a clinical trial of an investigational agent for treatment of COVID-19 infection.

Aldose reductase (AR), the first and rate-limiting step in the polyol pathway, is activated by hyperglycemic and ischemic conditions. AR initiates this pathway by catalyzing the NADPH-dependent reduction of the aldehyde form of glucose to produce sorbitol as an intermediate. Sorbitol is then oxidized using NAD to form fructose, catalyzed by the enzyme sorbitol dehydrogenase. Excess intracellular sorbitol produced by AR accumulates in cells, resulting in osmotic damage and ultimately cell death (figure 1).[4, 5]

Figure 1 Glucose Metabolism in the Polyol Pathway



Aldose Reductase plays a critical role in mediation of oxidative tissue damage in setting of inflammation induced by infection or ischemia.[6] A potent Aldose Reductase Inhibitor (ARI) with a favorable safety profile may be an important tool for short-term use in the clinical setting to prevent lung inflammatory damage and cardiomyopathy in patients with COVID-19 infection.[7, 8]

Aldose Reductase Inhibitors (ARIs), including the first-generation ARI zopolrestat, and the next generation ARI, AT-001 prevent oxidative-induced cardiac and lung injury in vivo and in vitro by preventing AR-induced downstream accumulation of reactive oxygen species and advanced glycation end-products. AT-001 has been shown to prevent oxidative damage to cardiomyocytes in oxidative-induced cardiomyopathies. AT-001 prevents ischemic/oxidative damage to cardiomyocytes in an ex-vivo system and decreases CK and other markers of cardiac damage In a Phase 1/2 clinical trial, AT-001 treatment in patients with Diabetic Cardiomyopathy decreased NTproBNP levels, a biomarker of cardiac stress or damage.

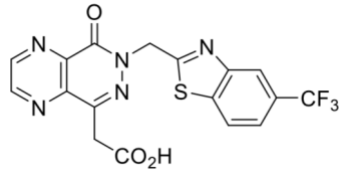
AT-001 demonstrates approximately 1,000-fold increased activity or potency vs. prior ARIs with excellent safety and tolerability profile. (see attach Investigator Brochure and Reference: Perfetti et al Overcoming the Safety Challenges of Aldose Reductase Inhibition: Development of AT-001 for Diabetic Cardiomyopathy; poster presented at WCIR Dec 2019; https://www.appliedtherapeutics.com/wp-content/uploads/2020/01/2019_WCIRDC_Poster_Final_1.pdf)

This interventional trial is intended to allow open-label emergency use of AT-001 for COVID-19 infected patients experiencing acute cardiopulmonary sequelae of disease.

2.2 Name and Description of the Investigational Agent

AT-001 is a small molecule with a molecular weight of 421 g/mol. Its chemical structure is provided below.

Chemical Structure of AT-001



AT-001 drug product is provided as AT-001 powder in a capsule in a 500 mg strength, packaged in blister cards. There are no excipients used in the manufacture of AT-001 powder in capsule, and no materials of human or animal origin are present. The white, opaque capsule shells contain hypromellose and titanium dioxide. AT-001 is currently in Phase 2/3 development for Diabetic Cardiomyopathy under IND 136043. Based on pre-clinical and clinical data presented in the Investigator Brochure, a dose of 1,500mg BID (3 X 500mg capsules twice daily) will be used.

AT-001 is an inhibitor of aldose reductase (AR), the first and rate-controlling enzyme of the polyol pathway which converts glucose to sorbitol and then to fructose. Hyperactivation of this pathway in patients with diabetes is thought to play a critical role in the pathogenesis of diabetic complications, including damage to peripheral nerves and blood vessels. Excess intracellular sorbitol produced by AR accumulates in cells, resulting in osmotic damage and ultimately cell death (Miki 2013). This pathological effect of excess sorbitol in cardiac cells can be seen in ventricular myocardial biopsies from diabetic patients which show significantly higher necrotic cardiomyocytes compared to biopsies from non-diabetic patients (Frustaci 2000).

In vitro assays demonstrate that AT-001 binds to AR with high affinity and specificity, and with no evidence of off-target effects. In in vivo animal studies, AT-001 normalized sorbitol levels in diabetic rats, prevented cardiac ischemic injury in diabetic mice, prevented acute cardiac ischemic injury in non-diabetic rats, and treated acute cardiac ischemic injury in non- diabetic rats.

2.2.1 Preclinical Data

A comprehensive program to evaluate the preclinical profile of AT-001 has been conducted to support the clinical development program. In vivo Good Laboratory Practice (GLP) safety pharmacology studies showed no effect of AT-001 on gross behavioral, physiological, or neurological function in rats (Irwin Test), and no cardiovascular or respiratory effects in dogs at doses up to 2000 mg/kg/day, the highest dose studied. The AT-001 oral toxicology program to date consists of two single-dose studies in rats, one single-dose study in dogs, a dose range finding study in rats, a dose range finding study in dogs, two definitive 28-day GLP studies (rats, dogs); and two chronic GLP toxicity studies conducted in rats (26 weeks) and dogs (39 weeks). In vitro and in vivo genotoxicity testing has been performed. Doses up to 2000 mg/kg/day have

been orally administered to rats and dogs for up to 39 weeks. In the single-dose studies, the MTD was considered to be 2000 mg/kg/day, since there were no findings in these studies. In the 28-day toxicology studies, the no adverse effect level (NOAEL) was determined to be 2000 mg/kg/day in both rats and dogs. Four reproductive studies of the effects of AT-001 have been conducted: 2 studies in rats (GLP) and 2 studies in rabbits (one non-GLP, one GLP). Based on these findings, the NOAEL for maternal and embryo/fetal developmental toxicity was 1000 mg/kg/day (the highest dosage level tested) in rats and 200 mg/kg/day in rabbits. AT-001 was shown to be negative for mutagenic activity in the reverse mutation assay, negative in the in vitro micronucleus assay, and negative in the in vivo micronucleus assay.

2.2.2 Clinical Data to Date

To date, one clinical study (AT-001.1001) has been conducted with AT-001. Full details are provided in the attached Investigator Brochure.

StudyAT-001-1001, the first in human study of AT-001, was a Phase 1-2, three-part, randomized, placebo-controlled study designed to assess the safety, tolerability, PK, and PD (effect on sorbitol) of AT-001 in adults with Type 2 Diabetes Mellitus (T2DM). Since AR converts glucose to sorbitol, and AR activity is elevated in diabetic patients, sorbitol normalization was examined as a PD biomarker of target engagement. The study had 3 parts: single ascending dose (SAD) (Part A), 7-day multiple ascending dose (MAD) (Part B), and a 28-day MAD extension part (Part C). A thorough safety review of each dose cohort was conducted prior to escalation to the next higher dose.

All doses and dosing regimens were well-tolerated with no safety issues identified. There were no serious adverse events (SAEs) considered treatment-related and no AEs causing discontinuation of study treatment. No clinically relevant changes in vital signs, ECG or clinical safety laboratory values were noted. AT-001 did not cause an increase in glucose levels and was not associated with adverse interactions with any concomitant diabetes medications used by patients during the study.
Mean AT-001 Tmax was between 1.5 to 3 hours, and mean half-life ranged between 1.2 to 3.4 hours across all SAD and MAD cohorts. The maximal and systemic exposure in terms of Cmax and AUC0-inf appear to increase with increasing dose in a dose proportional manner in SAD cohorts, as well as in MAD cohorts on Days 1, Day 7, and day 28. AT-001 did not accumulate in plasma following administration of daily doses for up to 28 days.

No clinical drug interaction studies have been conducted with AT-001 to date. The potential of AT-001 to inhibit the catalytic activities of key CYP isoforms was evaluated in an in vitro metabolism study using recombinant human CYP isoforms, while its potential to induce the catalytic activities of key CYP isoforms was evaluated in an ex vivo metabolism study using human hepatocytes. AT-001 over the concentration range tested (0.00545 to 50.0 μM) did not significantly inhibit human CYP450 isozymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 (midazolam and testosterone substrates). The induction of human CYP1A2, 2B6, and 3A4 by AT-001 at the highest concentration tested (100 μM), observed in one of the three lots of hepatocytes, was lower than that with the control inducers which produced effects in all lots of hepatocytes.

2.2.3 Dose Rationale (if applicable)

The 1500 mg twice daily dose is based on safety observations from the 28-day multiple ascending dose extension study.

2.3 Rationale

COVID-19 and previous coronaviruses associated with acute respiratory syndrome have high mortality rates, primarily attributable to respiratory failure and a substantial minority with cardiovascular complications. The proposed study will provide novel data in US patients to enhance cardiovascular risk prediction and identify potential novel therapies for therapy.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

In subjects enrolled in the prospective registry, the only risk is potential breach of confidentiality.

In subjects enrolled in the interventional trial, additional risk is associated with investigational agent. In the completed first in human study (Study AT-001.1001) AT-001 was generally well tolerated with no safety issues identified. There were no SAEs considered treatment-related and no AEs causing discontinuation of study treatment. No clinically relevant changes in vital signs, ECG or clinical safety laboratory values were noted.

Potential risks of AT-001 based on non-clinical data and previous experience with other aldose reductase inhibitors include:

- Acute hypersensitivity reactions
- Hepatic toxicity, including fatal hepatic necrosis
- Renal toxicity: Nephrolithiasis (calculi and pelvic dilation suggestive of an obstructive mechanism leading to development of pyelonephritis were reported in female rats in a 6-month chronic toxicology study. These renal findings were not reproduced in dogs in a 9-month chronic toxicology study)
- Gastrointestinal events, including nausea, vomiting, diarrhea, flatulence, abdominal pain
- Ocular effects (two cases of non-adverse, reversible multifocal pinpoint corneal opacities in a 28-day toxicology study in dogs, which was not reproduced in a 9- month chronic toxicology study)
- Hypotension and dizziness
- Skin rash/eczema
- Decreases in hemoglobin, erythrocyte count, and lymphocyte count
- Reduction in total protein in blood

The incidence of these side effects for short-term exposure to AT-001 in COVID-19 patients is unknown. We anticipate that patients with COVID-19 infection will receive concomitant treatments including off-label use of FDA-approved drugs, anti-viral therapy with remdesivir under expanded access or emergency use access, and treatment with hydroxychloroquine, convalescent sera, and/or IL-6 inhibitors within the context of clinical trials. Based on knowledge of the pathophysiology of COVID-19 infection and the pharmacology of AT-001, we do not anticipate that these concomitant medications will increase risk associated with AT-001. Patients with COVID-19 infection are known to be a high risk of complications including

multisystem organ failure (liver, kidney, heart, lung, hematological system, nervous system with associated laboratory abnormalities) and septic shock (hypotension with metabolic abnormalities). We will collect daily clinical information to monitor evidence of organ dysfunction and septic shock in the electronic CRF. We will identify potential AE related to study drug based upon temporal relationship with study drug administration, AE in the above list of potential AE associated with aldose reductase inhibition, or suspicion that the magnitude and/or duration of organ dysfunction and associated laboratory abnormalities is different from that expected due to COVID-19 infection alone. If treatment related AE are identified, the study drug may be discontinued per the discretion of the PI, Sponsor, and treating physician.

2.4.2 Known Potential Benefits

There is no direct benefit to subjects enrolled in the prospective registry.

Based on its known mechanism of action and observations in the first in human study, there is possible benefit to subjects who receive AT-001 in the interventional study.

3 Objectives and Purpose

3.1 Primary Objective

- Registry Study: To characterize serial measures cardiac structure and function and in-hospital survival in hospitalized patients with COVID-19 infection
- Interventional Trial: To characterize safety of AT-001 in hospitalized patients with COVID-19 infection

3.2 Secondary Objectives (if applicable)

- To develop predictive models of cardiac risk in hospitalized COVID-19 infection patients
- To assess safety of treatment with AT-001 plus standard of care on in-hospital survival in patients with COVID-19
- To characterize the effects of treatment with AT-001 plus standard of care on in-hospital mortality, progression of acute lung injury requiring mechanical ventilation, and serial measures of cardiac structure and function

4 Study Design and Endpoints

4.1 Description of Study Design

The proposed study is a prospective registry of patients hospitalized with COVID-19 infections at participating sites (NYU Tisch, NYU Brooklyn, NYU Winthrop, Bellevue Hospital Center). Clinical data related to the COVID-19 infection will be extracted from the electronic medical record as described below in patients who meet study entry criteria. To maintain confidentiality, all subjects will be assigned a unique study identifier number. De-identified data will be recorded in an electronic database (REDCap).

A subset of patients enrolled in the registry study may be eligible to participate in an open-label interventional trial of AT-001. For the substudy, informed consent will be obtained at the time of study entry, and clinical data will be extracted from the medical record using the same protocol

as the registry study. Additional safety and tolerability data will be collected for patients participating in the interventional trial.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Primary Endpoint for Registry Study: Proportion of subjects with decreased left ventricular ejection fraction ≥10% from baseline at time of hospitalization

Primary Endpoint for Embedded Clinical Trial: Safety of AT-001 based on adverse events reporting

4.2.2 Secondary Endpoints

Secondary Endpoints (for registry and clinical trial):

- Change in left ventricular ejection fraction
- Change in left ventricular end-diastolic diameter
- Change in left ventricular end-systolic diameter
- Change in biomarkers of cardiac injury
- Frequency of atrial fibrillation
- Frequency of heart block
- Frequency of non-sustained ventricular tachycardia
- Frequency of sustained ventricular tachycardia
- Frequency of ventricular fibrillation

Secondary Endpoints (for clinical trial):

- Proportion of subjects requiring mechanical ventilation
- Proportion of subjects with decrease in left ventricular ejection fraction ≥10% from baseline at time of hospitalization

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

Registry Study: In order to be eligible to participate in the registry study, an individual must meet all of the following criteria:

1. Age ≥18 years of age
2. Hospitalized at one of the participating NYULH locations
3. Confirmed COVID-19 infection

Interventional Study: In order to be eligible to participate in the registry study, and individual must meet all of the inclusion criteria of the registry study plus the following critieria:

1. Hospitalized at NYU Tisch or NYU Winthrop
2. History of diabetes mellitus or blood glucose measurement >126 mg/dl

AND

EITHER

3. History of hypertension and/or ischemic heart disease and/or heart failure

OR

4. Other co-morbid condition that in the opinion of the PI increases risk of heart or lung injury related to the aldose reductase pathway

5.2 Exclusion Criteria

Registry Study: An individual who meets any of the following criteria will be excluded from participation in the registry study:

1. Persons who have opted out of research participation at NYU
2. Pregnancy

Interventional study: An individual who meets any of the following criteria will be excluded from participation in the interventional study:

1. Persons who have opted out of research participation at NYU
2. Pregnancy
3. Women of childbearing potential
4. Breast-feeding women
5. Participation in another FDA-regulated investigational drug placebo-controlled clinical trial within previous 30 days
6. Hospital length of stay at time of study entry >14 days
7. Inability to comply with oral or nasogastric tube administration of study drug

Co-enrollment in other interventional studies in the COVID-19 population will be permitted if in the judgement of the PI and Sponsor, there is no anticipated increase in risk of exposure to AT-001 based on the known pathophysiology of COVID-19 infection and pharmacology of AT-001, and co-enrollment is permitted in the other protocol(s). Co-enrollment will be tracked at reported to the IRB and Sponsor.

5.3 Vulnerable Subjects

Critically-ill patients with COVID-19 may not have capacity to provide consent. The registry research is minimal risk without direct benefit. Waiver of consent and authorization are requested as is not feasible to obtain informed consent and HIPAA authorization from 500 subjects in order to conduct the prospective chart review for the registry component of the study. Although we will need access to the subjects' medical record for the duration of the study, an individual's PHI will be destroyed once they complete the study.

The primary treatment team, which consists of critical care physicians will determine subject capacity based on their interactions with the patient, presence of neurological complications, and use of sedative agents. These critical care physicians are qualified to assess capacity for consent as part of their clinical management of the patient. Subjects will be regularly assessed by the primary critical care team throughout the study to determine whether or not they have regained or lost the capacity to consent. If subjects who have the capacity to consent at the onset of the study lose capacity during the study, their legally authorized representative will be identified and consent sought for the subject's continued participation in the study. If subjects regain the capacity to consent during the study and decline to continue participation, state they will be asked if previously collected data can still be used. If they decline, this data will be discarded.

If the potential participant lacks capacity, the legally authorized representative (identified in accordance with NYS as the highest in priority of the following: court appointed LAR, health care proxy, spouse or domestic partner, adult son or daughter, parent, grandparent, adult grandchild who maintains regular contact with subject as to be familiar with subject's activities, health, or beliefs) will provide consent for the interventional study.

5.4 Strategies for Recruitment and Retention

Existing infection surveillance procedures identify all patients with COVID-19 admitted to the participating sites. These daily surveillance lists will be used to identify patients for the registry. Subjects potentially eligible for the interventional study will be identified by the intensivist in charge of patient care. The primary treatment team of critical care physicians will approach the patient and/or LAR regarding interest in participation in the study.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

The study will use DataCore and EPIC for recruitment purposes. All subjects with COVID-19 infectoins are tracked to specific hospital floors for infection control purposes. Patients who meet entry criteria on COVID-19 positive hospital floors will be identified by electronic chart review. The primary care team will be contacted to confirm that the patient is appropriate for the study and willing to be approached for research.

5.5 Duration of Study Participation

Duration of study participation for the registry study is until hospital discharge, or up to 30 days, whichever is shorter.

Duration of study participation for the interventional study is up to 30 days after last dose of AT-001.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 500 participants are enrolled in the registry, and approximately 20 participants in the interventional study.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

If a participant requests withdrawal from the study, all data collection will stop and all previously collected data will be deleted from the research database. Any analyses already completed at the time of the withdrawal request will remain unchanged.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

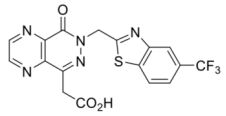
- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility
- Sponsor determination

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) Description

Product: AT-001 500mg capsule for oral administration
Dosage: 1,500mg (3X500mg capsules) twice daily
Mode of Administration: Oral
Compound:



Please see attached Sponsor pharmacy manual for additional details.

6.1.1 Acquisition

Investigational product will be shipped by the Sponsor and IND holder Applied Therapeutics Inc

6.1.2 Formulation, Appearance, Packaging, and Labeling

AT-001 drug product is provided as AT-001 powder in a capsule in a 500 mg strength, packaged in blister cards. There are no excipients used in the manufacture of AT-001 powder in capsule, and no materials of human or animal origin are present. The white, opaque capsule shells contain hypromellose and titanium dioxide.

6.1.3 Product Storage and Stability

The product is stable at room temperature

6.1.4 Preparation

None

6.1.5 Dosing and Administration

Three 500 mg capsules (1500 mg) twice daily

6.1.6 Route of Administration

Oral. For subjects unable to swallow capsules, the capsules will be opened to allow mixing with soft foods, or mixed with water for nasogastric tube administration.

6.1.7 Duration of Therapy

Up to 14 days per discretion of the investigators and treatment team

6.1.8 Tracking of Dose

Dosing will be tracked in EPIC per hospital nursing and pharmacy protocol

6.2 Study Agent Accountability Procedures

The investigational pharmacy will track Investigational product

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Study procedures include data collection from the electronic medical record. The data collection will be performed by automated data extraction and chart review, and will be recorded on de-identified electronic case report forms (see Appendix for eCRF).

7.1.2 Standard of Care Study Procedures

All participants will receive standard of care for COVID-19 infection. This includes supportive measures for symptomatic relief, assisted ventilation including use of sedatives, pharmacological management of shock, organ injury, co-morbid bacterial infections, and co-morbid conditions.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Standard of care laboratory procedures will be performed; results will be recorded in the research database There are no study-related laboratory evaluations.

- ***Hematology:*** *hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Biochemistry:*** *serum electrolytes, blood urine nitrogen, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total protein, calcium, magnesium, phosphate, troponin-I, brain natriuretic peptide, ferritin, CRP, ESR, IL-6, .*
- ***Urinalysis:*** *dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.*
- ***Pregnancy test****, usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.*

7.3 Study Schedule

Registry Study: All clinically-derived data on the attached eCRF will be collected on a daily basis until hospital discharge, or first 30 days of hospitalization (whichever is shorter).

Interventional study: All clinically-derived data on the attached eCRF will be collected on a daily basis during IP administration, with safety monitoring continuing 30 days after last dose of IP. In additional the following study procedures will be performed:

7.3.1 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain informed consent for potential participant (or their LAR) verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- See electronic case report form. These data will be collected at baseline.
- Start study drug administration
- Safety monitoring

7.3.2 Daily Interventional Study Visits (up to 14 days)

- See electronic case report form. These data will be collected daily.
- Study drug administration
- Safety monitoring

7.3.3 Final Study Visit

- Safety monitoring for 30 days after last dose of IP

7.3.4 Withdrawal/Early Termination Visit

See electronic case report form

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.4.1 Precautionary Medications, Treatments, and Procedures

None

7.5 Prohibited Medications, Treatments, and Procedures

Other investigational medications

7.6 Prophylactic Medications, Treatments, and Procedures

None

7.7 Rescue Medications, Treatments, and Procedures

None

7.8 Participant Access to Study Agent at Study Closure

None

8 Assessment of Safety

8.1 Specification of Safety Parameters

All subjects in the interventional study will be observed daily by the treatment team for detection of adverse events.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

8.2.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs

will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Adverse events that do not meet criteria for serious adverse event or unanticipated event will be submitted at the time of study continuation or termination, whichever occurs first.

8.4.2 Serious Adverse Event Reporting

According to CFR 21 CFR 312.32(c)(1), "the sponsor must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies reporting. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected

adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
(B) 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 (e.g., tendon rupture);
(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."

Furthermore, according to 21 CFR 312.32(c)(2), "the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) within 72 hours of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

Pregnancy will be considered an unanticipated event and will be reported to the IRB and Sponsor within 24 hours.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Study Halting Rules

Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the Sponsor.

8.7 Safety Oversight

It is the responsibility of the Principal Investigator and Sponsor to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. The data safety monitoring plan will consist of daily review of the clinical and laboratory data recorded in the attached electronic CRF. Medical monitoring will include a regular assessment of the number and type of serious adverse events with complete review of the clinical course of each subject after 7 and 14 days of treatment. Due to the nature of COVID-19 infection, many events related to organ dysfunction and septic shock are anticipated in this population. Only suspected treatment related adverse events, based on temporal relationship, biological plausibility of relation to aldose reductase inhibition, or magnitude/duration greater than anticipated from COVID-19 alone will be reported. A summary of the outcomes of these reviews will be submitted to the IRB at the time of continuation application, or sooner if protocol modifications are required for subject safety.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- The PI will oversee the monitoring for data integrity for this study.
- Independent audits will not be conducted to ensure monitoring practices are performed consistently across all participating sites.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

Due to the urgent COVID-19 crisis, there is no formal SAP.

10.2 Statistical Hypotheses

The null hypothesis for the registry study is that there are no significant associations between clinical characteristics at study entry and subsequent occurrence of cardiac dysfunction, lung dysfunction or death in hospitalized patients with COVID-19 infection.

There will be no hypothesis testing for the interventional trial. The primary endpoint is safety of AT-001 based on descriptive statistics and qualitative evaluation of adverse event monitoring. Descriptive statistics will be used to assess frequency of secondary endpoints without hypothesis testing.

10.3 Analysis Datasets

The registry dataset consists of all subjects with any entered data.
The interventional safety data set will be all subjects who received at least one dose of AT-001

10.4 Description of Statistical Methods

10.4.1 General Approach

Descriptive statistics will be used to define data missingness, data distributions.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

Registry Study

- Multivariable logistic regression models and Cox Proportional Hazard models will be used to estimate the association between clinical variables at time of hospital admission and ICU admission with proportion of patients with decreased left ventricular ejection fraction ≥10% and secondary endpoints cardiac structure and function.

- Multivariable mixed models will be used to estimate the association between serial measures of cardiac structure and function, need for mechanical ventilation, and in-hospital mortality.

Interventional Study

- Safety assessment of AT-001 based on reported adverse events
- Exploratory analyses with descriptive statistics to estimate effects of co-enrollment on safety outcomes
- Exploratory analyses with descriptive statistics to describe clinical outcomes in patients treated

10.4.3 Analysis of the Secondary Endpoint(s)

The same analyses will be used for secondary endpoints.

10.4.4 Safety Analyses

Adverse events will be analyzed as summary statistics and coded by MedDRA.

10.4.5 Adherence and Retention Analyses

Data missingness will be assessed with descriptive statistics.

10.4.6 Baseline Descriptive Statistics

Baseline characteristics will be summarized with non-parametric statistics

10.5 Sample Size

The estimated sample size for the registry (500 participants) and the interventional trial (20 participants) are convenience samples based on the anticipated number of patients at NYU with COVID-19 infection. These numbers should provide sufficient power to conduct the regression analyses for the registry (up to 50 predictor variables), and for safety assessment of AT-001.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should

be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

In the event that the participant is critically ill and unable to provide consent, a study team member may conduct the informed consent process via telephone or video (webex) with use of e-consent through REDCap to obtain and document informed consent from the subject/LAR.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and/or LAR and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

In the event that the participant is not able to provide consent due to temporary loss of capacity during critical illness, the LAR will provide consent.

13.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

13.5 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period. The research record data will be securely stored on the NYU REDCap database with password controlled access limited to authorized study personnel. The research record will not contain any identifiers. Each subject will be assigned a random study ID number. The link between the subject PHI and the study ID number will be maintained by the PI on encrypted shared drives maintained NYU and in the study binder which is kept in a locked cabinet in a locked room.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify DCC>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to the Sponsor and IRB.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

Applied Therapeutics, Inc.

15.2 Costs to the Participant

None

15.3 Participant Reimbursements or Payments

None

16 Study Administration

16.1 Study Leadership

The Sponsor and PI will lead the study at NYU.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the <specify NIH IC> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Sponsor Investigator Brochure
- Sponsor Emergency use IND protocol
- Sponsor Pharmacy Manual
- eCRF for data collection

20 Schedule of Events

Activity	Daily Data Collection during hospitalization	Interventional Trial Entry	Interventional Trial Daily Procedures (up to 14 days)
Study team procedures			
Consent		X	
eCRF completion	X	X	X
Study drug/device dispensation		X	X
Safety Monitoring (until 30 days after last dose of IP)		X	X