A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AT-527 in Subjects with Moderate COVID-19

Sponsor Protocol Number: AT-03A-001

Investigational Product(s): AT-527

Sponsor:

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COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

Protocol Version		Date
9.0	**Amendment 8**	**26-Aug-2021**

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SYNOPSIS

Protocol Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AT-527 in Subjects with Moderate COVID-19
Protocol Number:	AT-03A-001
Clinical Phase:	2
Objectives:	• Evaluate safety and efficacy of AT-527 in subjects with moderate COVID-19 disease and risk factors for poor outcomes. • Primary objective for Part A: reduce progressive respiratory insufficiency (PRI) by at least 50% in a population that is at high risk for PRI. • Primary objective for Part B: evaluate the antiviral activity of AT-527 compared with placebo
Safety Assessment:	Assessing safety and tolerability of AT-527 at the selected doses will be an important objective of the study. • Adverse events (AEs), blood oxygen saturation (SpO2), vital signs, physical examination, electrocardiogram (ECG) monitoring, standard safety laboratory tests, respiratory deterioration to requirement for mechanical ventilation
Efficacy Assessments:	**Primary efficacy endpoint:** • Part A (secondary for Part B): The primary efficacy endpoint is PRI, defined as a ≥ 2-tier increase in respiratory support methods required to maintain satisfactory oxygenation (SpO2 ≥ 93%), using a 6-tier hierarchical scale of respiratory support methods, within the 14-day study period. The primary efficacy goal is a 50% reduction in the incidence of PRI in active treatment recipients compared to placebo recipients. • Part B (secondary for Part A): Change from baseline in amount of SARS-CoV-2 virus RNA as measured by RT-PCR over time. **Secondary efficacy endpoints (Parts A and B):** • Median time (days) to Clinical Recovery, using an adapted National Institute of Allergy and Infectious Diseases (NIAID) ordinal scale of Clinical Status. The goal for active treatment is to reduce the median time to Clinical Recovery (status 6,7, or 8 in the NIAID Clinical Status scale) by at least 4 days. • Proportion of subjects experiencing respiratory failure or death • Change (improvement vs. worsening) in the NIAID ordinal scale of overall Clinical Status • All-cause mortality • Duration of hospitalization/confinement for COVID-19 • Time to sustained non-detectable SARS-CoV-2 virus in nose/throat • Proportion of subjects who are still SARS-CoV-2 positive over time
PK Assessment:	• Plasma concentrations of AT-527 and its metabolites evaluated by sparse PK sampling
Study Design:	• Adult subjects, ≥18 years of age, who are hospitalized/confined with moderate COVID-19 and not on a ventilator. • Subjects must be diagnosed with COVID-19 (SARS-CoV-2 positive) by a standard assay or equivalent testing.

- Note: SARS-CoV-2 infection will be confirmed at Screening and assessed during the study with an FDA Emergency Use Authorization (EUA)-approved assay.
- Moderate disease defined by the following:
  - Symptoms of COVID-19, with initial symptom onset within 5 days prior to Screening:
    - At least 1 of the following: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
  - Clinical signs indicative of COVID-19 (as above), with:
    - SpO2 ≥ 93% on room air or requires ≤ 2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥ 93%
- Subjects must also have at least one of the following known risk factors for poor outcomes: obesity (BMI>30), hypertension, diabetes, asthma
- Randomized, double-blind, placebo-controlled study
- Blinded study treatment: AT-527 or matching placebo for 5 days in combination with supportive standard of care (SOC) treatments per local SOC policies

The study will be conducted in 2 Parts. Part A will evaluate an AT-527 dose of 550 mg BID for 5 days and Part B will evaluate a dose of 1100 mg BID for 5 days. Based on the interim analysis conducted after Part A (which demonstrated a positive antiviral signal but low disease progression rates in the population), Part B was added via an amendment with a virologic primary endpoint.

- Part A subjects will be randomized (1:1) to one of the two following arms:

Disease Severity	Treatment Duration	Dosing Arms	
Moderate	5 days	active	550 mg AT-527 administered every ~12 hours (10 doses) + SOC
		placebo	AT-527 placebo administered every ~12 hours (10 doses) + SOC

*Randomized 1:1 (active:placebo)

- A cohort of 20 subjects will initially be enrolled to preliminarily assess the safety of the 550 mg twice daily (BID) dosing regimen. Enrollment will be paused after the first 20 subjects, until the data safety monitoring board (DSMB) conducts a safety review. If study stopping criteria are not met, a second cohort of 20 subjects will be enrolled. Again, enrollment will be paused until the DSMB conducts a safety review of these data.
- Part A enrollment was paused after 81 subjects were randomized. No additional subjects will be randomized in Part A.
- Part B subjects will be randomized (1:1) to one of the two following arms:

Disease Severity	Treatment Duration	Dosing Arms

	<table><tr><td rowspan="2">Moderate</td><td rowspan="2">5 days</td><td>active</td><td>1100 mg AT-527 administered every ~12 hours (10 doses) + SOC</td></tr><tr><td>placebo</td><td>AT-527 placebo administered every ~12 hours (10 doses) + SOC</td></tr></table> *Randomized 1:1 (active:placebo) • Up to an additional 110 subjects will be enrolled in Part B. • An additional DSMB safety review will occur when 50% of the Part B subjects have been enrolled. <u>Key Study Design Features</u> • An independent DSMB will be established for safety monitoring. • Sponsor, CRO, and site personnel will remain treatment-blinded to all DSMB analyses unless the DSMB alerts the Sponsor to significant recommendations regarding study discontinuation for efficacy, safety, or futility reasons.
Duration of Study:	• The primary study period is 14 days from randomization. • Additional follow-up data will be obtained at 7 days, 14 days and 49 days after primary study completion at Day 14.

Number of Subjects:	• Targeted study enrollment is up to 190 eligible COVID-19 subjects.
	  ○ Part A: 81 subjects were randomized at the time of the Part A interim analysis.
	  ○ Part B: Up to an additional 110 subjects will be enrolled in Part B.

Inclusion Criteria:	1. Willing and able to provide informed consent.
	2. Male or female subjects ≥18 years of age.
	3. Subject is hospitalized or in a hospital-affiliated confinement facility for which the principal investigator is credentialed and study staff have access to study participants and their data.
	4. Subject must be diagnosed with COVID-19 (SARS-CoV-2 positive) by a standard assay or equivalent testing. *Note: SARS-CoV-2 infection will be confirmed with an FDA EUA-approved assay.*
	5. Moderate disease defined by the following:
	  • Symptoms of COVID-19, with initial symptom onset within 5 days prior to Screening:
	  • At least 1 of the following: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
	  • Clinical signs indicative of COVID-19 (as above), with:
	  • SpO2 ≥ 93% on room air or requires ≤ 2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥ 93%
	6. Subjects must also have at least one of the following known risk factors for poor outcomes: obesity (BMI>30), hypertension, diabetes or asthma.
	7. QTcF interval ≤ 450 ms for males and ≤ 460 ms for females at Screening.
	8. Females of childbearing potential must agree to use protocol specified methods of contraception as described in Section 5.9.
	9. Females of childbearing potential must have a negative pregnancy test at Screening.
	10. Subject must be able to take oral tablet medications.

	11. Subject is, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements.
Exclusion Criteria:	1. Female subject is pregnant or breastfeeding. 2. Clinical signs indicative of severe or critical COVID-19 illness, defined as any of the following: RR ≥30, HR ≥125, SpO2 <93% on room air or requires >2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥93%, systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg or PaO2/FiO2 <300 3. Any subject with a concomitant life-threatening condition, including but not limited to the following: requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), acute respiratory distress syndrome (ARDS), shock, cardiac failure or suspected bacterial sepsis. 4. Evidence of lobar or segmental consolidation on chest imaging. 5. Congestive heart failure or myocardial infarction within the previous 6 months. 6. Recurrent nausea, vomiting or known malabsorption syndrome, that would interfere with oral medication treatment. 7. Creatinine clearance < 60 mL/min (Cockcroft-Gault formula) 8. Abuse of drugs or alcohol that could interfere with adherence to study requirements as judged by the investigator. 9. Treatment with other drugs thought to possibly have activity against SARS-CoV-2. *Note: If the subject was previously treated with such an agent, treatment must have been discontinued at least 7 days prior to planned dosing on the current trial. The use of hydroxychloroquine is not allowed in this trial. Convalescent plasma is permitted as part of local SOC.* 10. Use of other investigational drugs within 30 days of dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study. 11. S-T segment elevation or other clinically significant abnormal ECG at Screening, as determined by the investigator. 12. Subject has a history of active hepatitis B infection or uncured hepatitis C infection. Subjects with human immunodeficiency virus (HIV) infection are allowed, as long as they are virologically suppressed with CD4 count at least 500 cells/mm^3. 13. Active clinically significant diseases including: ▪ Active urinary tract infection ▪ History of severe renal impairment or receiving renal replacement therapy (hemodialysis, peritoneal dialysis) 14. Subjects with malignant disease can continue antineoplastic therapy during the study period *unless* the antineoplastic therapy includes an immunomodulator or is expected to result in severe bone marrow suppression during the study (e.g., risk for grade 3 or higher anemia, leukopenia, or thrombocytopenia). 15. Requires use of immunosuppressive doses of systemic corticosteroids, defined as the equivalent of 20 mg prednisone daily during any two week time period (280 mg prednisone equivalent total dose) in the three months prior to study entry. Standard of care dexamethasone indication and dosing are permitted if needed for treatment of COVID-19 Syndrome. 16. Requires use of immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions) during the primary 14-day study period. 17. Requirement of any prohibited medications (Section 5.8).

	18. Abnormal values at Screening: ▪ ALT or AST > 5 x upper limit of normal (ULN) ▪ Total bilirubin > 1.5 x ULN, unless the subject has known Gilbert's syndrome ▪ Hemoglobin < 10 g/dL for females or < 12 g/dL for males ▪ Total white blood cell (WBC) count < 2,500/mm^3 or absolute neutrophil count < 800/mm^3 ▪ Platelet count < 80 x 10^9/L 19. Any clinically significant medical condition or laboratory abnormality that, in the opinion of the investigator, could jeopardize the safety of the subject or impact subject compliance or safety/efficacy observations in the study. 20. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 14 visit.
Test Product:	• AT-527 will be provided as 550 mg tablets • Matching placebo tablets will also be provided.
Dose and Mode of Administration:	• Study drugs (AT-527 or placebo) to be administered orally • Doses and frequency as described in the protocol
Statistical Methods:	Sample size calculations and power statements were performed using SAS/STAT v9.4 (SAS Institute Inc., Cary, NC, USA). All analyses will be performed in this version of SAS/STAT or higher unless otherwise noted in the Statistical Analysis Plan (SAP). Efficacy analyses will be performed on the intent-to-treat (ITT) population, which is defined as all randomized patients. Unless otherwise indicated, efficacy analyses will be carried out separately for Part A and Part B. An interim analysis was carried out on the first 70 subjects randomized in Part A. Prior to conducting the interim analysis, a low overall PRI event rate was observed in the blinded aggregate dataset, indicating that it was likely that the initial powering assumptions for the primary endpoint were no longer reasonable and the study, as originally planned, would be unlikely to provide a sensitive assessment of the PRI endpoint. Consequently, it was decided to continue the study (i.e Part B), exploring a higher dose with a change in the primary endpoint to be based on SARS-CoV-2 virus RNA as measured by RT-PCR on nasopharyngeal swab samples. <u>Primary efficacy endpoint:</u> ***Part A*** The primary endpoint of the study is the proportion of subjects with PRI. Proportions of subjects (active or placebo-treated) with PRI until Day 14 will be compared by study arm. The Cochran Mantel Haenszel (CMH) test, adjusting for randomization strata, will be performed to compare the proportion of PRI rate (PRIR) in study arms. Assuming PRIR rates of 0.4 and 0.2 in the placebo and experimental arms, respectively, and testing at alpha one-sided of 0.025 with power of 0.8, a total of 182 subjects are required at a 1:1 allocation, i.e. 91 per study arm. Per Amendment 8, Part A will conclude and enrollment will continue in Part B.

	Part B The primary endpoint of Part B is the change from baseline in amount of SARS-CoV-2 virus RNA (viral load) as measured by RT-PCR. Viral load will be assessed quantitatively using a validated assay. Analyses will be carried out at each scheduled time point. Part B of the study is signal seeking. The primary analysis aims to identify and characterize any potential effect of AT-527 on viral load over time. Analyses and p-values are descriptive and no adjustment for multiple comparisons will be made. Change from baseline viral load at each timepoint will be compared between the AT-527 group and the placebo group ANCOVA with treatment as a factor and log10 baseline viral load as a covariate. In the interim analysis of the first 70 subjects from part A, the observed AT-527 effect at Day 2 was a reduction of 0.7 log10 copies/mL relative to placebo. Assuming a standard deviation for change from baseline of 1.8 $\log_{10}$ copies/mL and 90% of Part B planned randomized patients eligible for analysis (i.e. 100 patients), there is at least 90% power to detect a true treatment effect of 0.7 using a one-sided test at 0.1 level of significance. Only patients with a positive qualitative SARS-CoV-2 RT-PCR test result at baseline will be included in this analysis. The least squares mean (LSM) change and its standard error of means (SE) in each group, the differences between two groups in LSM change with corresponding 95% confidence intervals (CIs), and p-values will be presented. <u>Key secondary endpoints:</u> The efficacy endpoint assessments are hierarchical in Part A. The key secondary endpoints will be tested, in order, only if the primary efficacy endpoint meets its success criteria and each higher endpoint meets its success criteria. This hierarchical testing strategy will preserve study alpha. The key secondary endpoints for Part A are indicated below with the hierarchical ordering. The hierarchical ordering pertains to Part A only. Following the change in protocol following the interim analysis, there will be no formal procedure to preserve study-wise type I error in Part B. All analyses are descriptive, and any findings would need to be confirmed in another study with prospective alpha control. With the change in primary endpoint in Part B, the primary endpoint and non-virological key secondary endpoints from Part A will be considered as key secondary endpoints in Part B. • First key secondary endpoint (Part A only): change from baseline in amount of SARS-CoV-2 virus RNA (viral load) as measured by RT-PCR. Viral load will be assessed quantitatively using a validated assay. Change from baseline viral load will be compared between the AT-527 group and the placebo group at scheduled time points using ANCOVA with treatment as a factor and log10 baseline viral load as a covariate. The least squares mean (LSM) change and its standard error of means (SE) in each group, the differences between two groups in LSM change with corresponding 95% confidence intervals (CIs), and p-values will be presented. Statistical significance at Day 5 will be assessed using a one-sided 0.025 level test. If the Day 5 comparison is significant, then the Day 2 treatment effect would be tested. • Second key secondary endpoint: median time (days) to Clinical Recovery from randomization, based on achieving disease resolution (status 6,7, or 8) in the NIAID Clinical Status scale

	The planned statistical comparison will use the Wilcoxon Mann-Whitney test with one-sided alpha=0.025. Patients without observed clinical recovery will have clinical recovery time assigned as 15 days to preserve the ranks for the comparison. • Third key secondary endpoint: respiratory failure or death A key secondary endpoint is the proportion of subjects with respiratory failure or death (RFD) in the first 28 study days. Treatments will be compared using the same methodology as that for the primary efficacy endpoint. To allow for a modest number of dropouts and subjects not testing positive for SARS-CoV-2 at baseline, the study enrollment goal will be 190 subjects. Additional efficacy assessments include: • Change (improvement vs worsening) in the NIAID ordinal scale of overall Clinical Status • All-cause mortality • Duration of hospitalization/confinement for COVID-19 • Time to sustained non-detectable SARS-CoV-2 RNA from randomization • Proportion of subjects who are still SARS-CoV-2 positive at Days 5 and 14

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
AST	Aspartate aminotransferase
BID	Bis in die; twice daily
BiPAP	Bi-level positive airway pressure
BMI	Body mass index
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CBC	Complete blood counts
CK	Creatine kinase
C_{max}	Maximum observed plasma concentration
CMH	Cochran Mantel Haenszel
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRO	Contract research organization
DAIDS	Division of AIDS
dNHBE	Differentiated normal human bronchial epithelial
DSMB	Data safety monitoring board
EC_{90}	90% effective concentration
eCRF	Electronic case report form
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic Data Capture
ET	Early termination
EU	European Union
EUA	Emergency use authorization
FDA	Food and Drug Administration
FiO2	Fraction of inspired oxygen
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
HAE	Human airway epithelial
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCO_3-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate or Hazard ratio
Huh-7	Human hepatoma cell line
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to treat

IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MCV	Mean corpuscular volume
MDCR	Median days to clinical recovery
MedDRA	Medical dictionary for regulatory activities
MERS	Middle East Respiratory Syndrome
NHP	Nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	No observed adverse effect level(s)
NT-proBNP	N-terminal pro b-type natriuretic peptide
P-gp	P-glycoprotein
PaO2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetics
POLRMT	Mitochondrial RNA polymerase
PP	Per protocol
PRI	Progressive respiratory insufficiency
PRIR	Progressive respiratory insufficiency rate
PT	Prothrombin time
QTcF	QT interval with Fridericia's correction
RFD	Respiratory failure or death
RFDR	Respiratory failure or death rate
RR	Respiratory rate
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SOC	Standard of care; System organ class
SOP	Standard Operating Procedure
SpO2	Blood oxygen saturation
TC	Telephone contact
TP	Triphosphate
ULN	Upper limit normal
WBC	White blood cell

SPONSOR PROTOCOL APPROVAL

Protocol Number: *AT-03A-001*

TITLE: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AT-527 in Subjects with Moderate COVID-19

On behalf of the Sponsor, we have read this study protocol and agree with its contents:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 8/27/2021 | 12:53:02 PM EDT
[redacted]6A77546D48B9728C389BBF8DF
[redacted]

8/27/2021

Date (dd-mmm-yyyy)

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 8/27/2021 | 10:04:23 AM PDT
[redacted]9D4B04AB435948FED9F4B6
[redacted]

8/27/2021

Date (dd-mmm-yyyy)

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Signer Name [redacted]
Signing Reason: I approve this document
[redacted]ing Time: 8/27/2021 | 1:54:48 PM EDT
[redacted]4FF1498EA550A47887014AB1
[redacted]

8/27/2021

Date (dd-mmm-yyyy)

Protocol Number: AT-03A-001

PRINCIPAL INVESTIGATOR PROTOCOL APPROVAL

Protocol Number: *AT-03A-001*

TITLE: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AT-527 in Subjects with Moderate COVID-19

I have read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with Good Clinical Practices and the applicable regulatory requirements:

_____ _____

Signature
Principal Investigator

Date (dd-mmm-yyyy)

_____

Printed Name
Principal Investigator

1. INTRODUCTION

1.1. Background

In December 2019, a cluster of patients in Wuhan, China were diagnosed with pneumonia with symptoms similar to the severe acute respiratory syndrome (SARS) outbreak in 2002-2003. Early in January 2020, the causative agent, a novel coronavirus now named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified. This virus has close RNA sequence homology to SARS-CoV, the name for the virus associated with the 2002-2003 SARS outbreak. The new life-threatening coronavirus, SARS-CoV-2, causes a potentially severe disease now called coronavirus disease 2019 (COVID-19), which has rapidly spread across the world. The COVID-19 outbreak was categorized as a pandemic by the World Health Organization (WHO) on 11 March 2020.

COVID-19 is an acute febrile respiratory disease that is usually mild-moderate in clinical severity but can be severe or fatal. Aside from fever and dry cough, many patients find the other common acute symptoms (fatigue/malaise, dyspnea/chest tightness, headache, myalgias, and gastrointestinal disturbance) to be very uncomfortable for 5-10 days or more, and some require hospitalization for close observation and supportive care. The acute COVID-19 clinical syndrome spontaneously resolves in most affected individuals (≥ 80%), but COVID-19 can be clinically severe, leading to a need for respiratory support (supplemental oxygen or even mechanical ventilation) in about 15-20% of patients, more in some series. Aside from respiratory insufficiency, accumulating COVID-19 clinical reports indicate an accompanying hyper-coagulopathy in many patients, resulting in thromboembolic processes that can damage any body organ, with reports of severe cardiac events, renal failure, liver damage, central nervous system events, and other disease manifestations. Reports of clinical features of COVID-19 patient populations have indicated common risk factors for poor outcomes, i.e.: older age (e.g., > 45 years), obesity, hypertension, diabetes, and chronic lung conditions (asthma, chronic obstructive pulmonary disease (COPD)) (Goyal P, et al. 2020). Progression to respiratory failure, with a need for mechanical ventilation, is common in the more severely ill COVID-19 patients, especially patients with the aforementioned risk factors, and is associated with a high risk of death. In two reports involving non-U.S. patients, 81-97% of patients who progressed to needing mechanical ventilation died, while a report on 24 early U.S. patients in Seattle ICU care indicated ≥ 50% mortality for ventilated patients (Weiss P and Murdoch DR 2020; Bhatraju PK, et al. 2020).

As of 28 June 2021, almost 180.5 million cases of COVID-19 and approximately 3.9 million COVID-19-related deaths were reported in over 200 countries and territories worldwide (World Health Organization 2021). The ~2% mortality rates for COVID-19 are lower than the 9.6% fatality rate observed during the 2003-2003 SARS outbreak, but fatality rates for both “SARS-1” and the current “SARS-2” (COVID-19) are well above the average 0.1% mortality rate observed year-on-year with globally recurring Influenza A pandemics.

Prevention and control of SARS-CoV-2 infection have focused on public health measures to slow transmission, such as social distancing, the use of face masks, and national or regional lockdowns. A number of vaccines have recently been approved for the prevention of SARS-CoV-2 infection, but these vaccines remain in the distribution phase and there are logistical challenges in vaccinating large populations globally. Additionally, the duration of protection

afforded by these vaccines as well as coverage of emerging variants is currently unknown. Intravenous remdesivir, an inhibitor of RNA-dependent RNA polymerase, and dexamethasone have shown benefit in hospitalized patients with severe COVID-19. However, in patients with moderate COVID-19, dexamethasone is not efficacious (and may be harmful) and the use of remdesivir is not approved for non-hospitalized patients (Gandhi et al. 2020). Since the initiation of the AT-03A-001 study, virus-neutralizing monoclonal antibody therapies [including sotrovimab, bamlanivimab plus etesevimab (with subsequent pause in distribution in the US), and casirivimab plus imdevimab] have been authorized for use in various regions (through emergency use authorization (EUA) in the US or conditional approvals in the EU). These monoclonal antibody therapies are not generally authorized for use in patients who are hospitalized due to COVID-19; they are administered intravenously (IV) in a hospital setting and are indicated for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years and older weighing at least 40 kilograms) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Thus, there may be some overlap in the AT-03A-001 population for those high-risk patients with moderate disease who are confined (instead of hospitalized for COVID-19). Access to treatment (remdesivir and monoclonal antibody therapies) and standard of care will be variable in each participating country.

Atea Pharmaceuticals is developing AT-527, a unique 6-modified purine nucleotide prodrug that, in laboratory studies, potently inhibits the RNA-dependent RNA polymerases of several single-stranded RNA viruses (e.g. flaviviruses [HCV, dengue] and coronaviruses). AT-527 demonstrated sub-micromolar potency against a range of coronaviruses, including SARS-CoV-1 (90% inhibitory concentration (EC_{90})=0.34 μM) and SARS-CoV-2 (mean EC_{90}=0.5 μM), as described in Section 4 of the AT-527 Investigator's Brochure. AT-527 can be administered orally once- or twice-daily, as tablets, and was previously in Phase 1-2a clinical testing for the treatment of chronic hepatitis C virus (HCV) patients. For that clinical testing program, comprehensive non-clinical studies were completed, which included 13-week repeat-dose animal toxicology studies conducted to Good Laboratory Practice (GLP) standards in two animal species (rat and monkey), to support long-term (up to 12 week) dosing in clinical studies. Supported by these and other non-clinical data, AT-527 has already been evaluated in two completed clinical studies involving healthy human volunteers and HCV patients. In a recently completed Phase 2 study, AT-527 was well-tolerated for durations up to 12 weeks in HCV-infected subjects and achieved a high rate of antiviral efficacy, with no safety/tolerance issues. In healthy and HCV-infected subjects, AT-527 exhibited a predictable and predictive pharmacokinetic (PK)/pharmacodynamic (PD) profile associated with the observed antiviral efficacy in HCV patients. This supportive human PK profile is likely to be observed with dosing of COVID-19 patients and is expected to be sufficient for achieving antiviral efficacy with AT-527 dosing of COVID-19 patients, based on the sub-micromolar EC_{90} for the active triphosphate of AT-527 against SARS-CoV-2 virus replication in laboratory studies.

The demonstrated clinical safety/tolerability of AT-527 in HCV patients, with an established supportive human PK profile, coupled with the potent *in vitro* activity of AT-527 against SARS-CoV-2, provide a strong scientific rationale to rigorously evaluate AT-527 in COVID-19 patients.

In the current phase 2 study, the safety, antiviral activity and efficacy of AT-527 will be evaluated in adult subjects (≥18 years of age) with risk factors for poor outcomes. Preventing

disease progression to successive stages of respiratory insufficiency is potentially lifesaving, as ultimate progression to dependence on intubated respiratory support is associated with a high rate of fatal outcomes (over 50% in U.S. patients, and over 80% in ex-U.S. patients, as noted above).

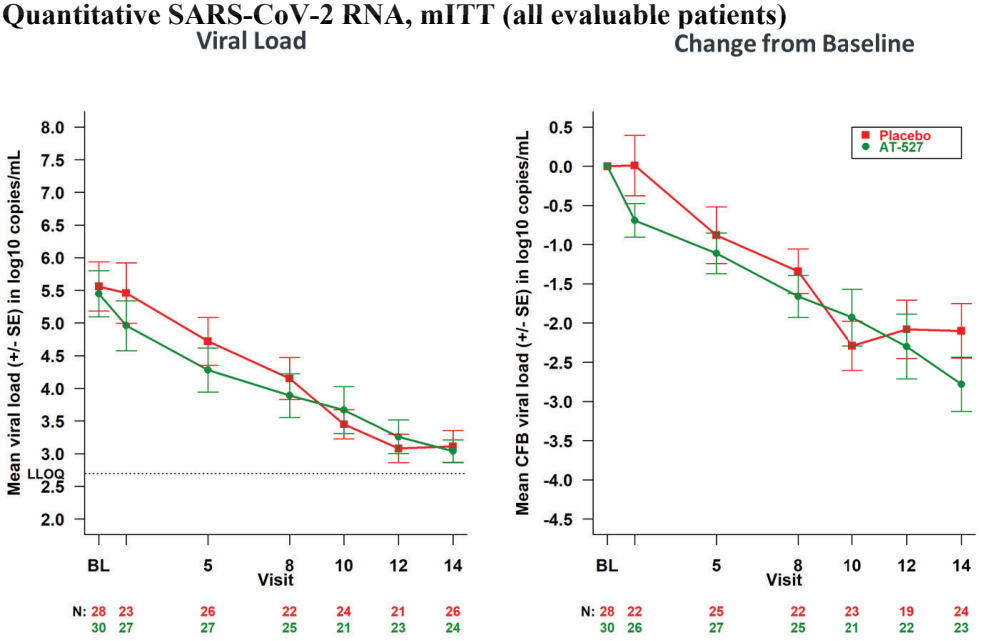
Additional information for AT-527 can be found in the AT-527 Investigator's Brochure.

Rationale/Background for Amendment 8

The clinical development program has been designed on the basis of the emergency nature of the ongoing pandemic. Although the initial primary efficacy goal of the originally designed study was to significantly reduce progressive respiratory insufficiency (PRI), it has become apparent, from blinded analysis, that the background rates of disease progression in this targeted study population are too low to demonstrate clinical efficacy differences between the treatment arms. With a better understanding of the disease resulting in improvements in patient management over time, the disease progression rates observed in this study are much less than the initial assumptions made at the beginning of the study/pandemic, which postulated that 40% of placebo recipients would progress and experience PRI. Due to the low progression rates and in order to support interactions with regulatory agencies, the Sponsor decided to pause enrolment and conduct an interim analysis during the course of the study.

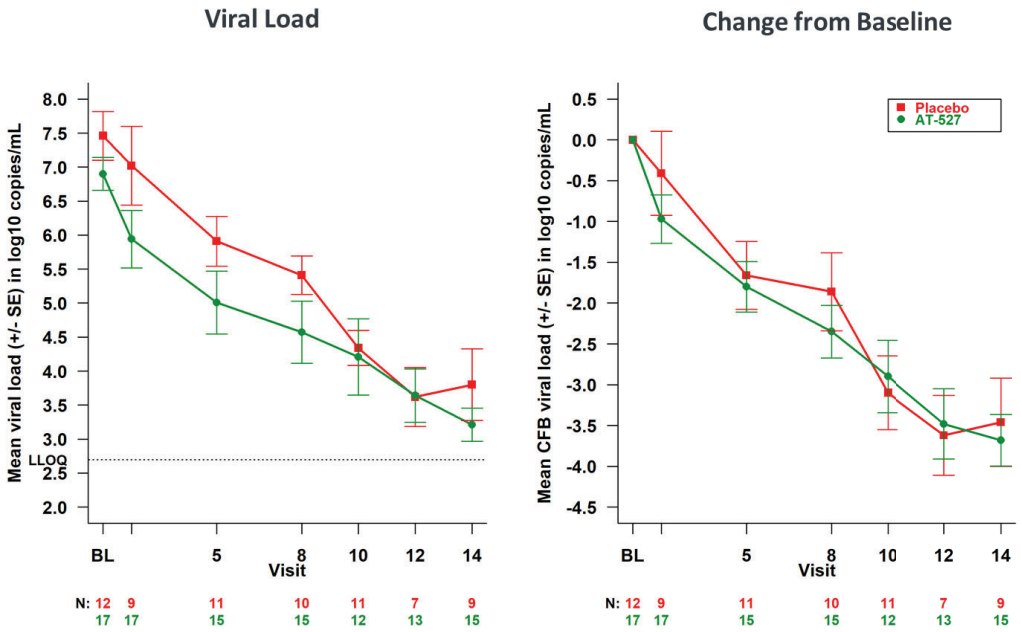
Enrollment in the study was paused after the 81st patient was randomized and the interim analysis (in which the study team remained blinded to individual treatment assignment) was performed on the first 70 patients who completed through Day 14 of the study. Of 62 patients evaluable for the virology analysis, 58 had baseline quantitative viral load data. This interim analysis indicated that AT-527 rapidly reduced viral load levels. At Day 2, patients receiving AT-527 experienced a 0.7 $\log_{10}$ greater mean reduction from baseline viral load as compared to placebo. A sustained difference in viral load reduction was maintained through Day 8 (see figure below). After Day 8, the curves in the groups converge, however, this is expected considering the natural history of the disease in which viral load generally peaks at the time of symptom onset and decreases spontaneously with time.

Quantitative SARS-CoV-2 RNA, mITT (all evaluable patients)



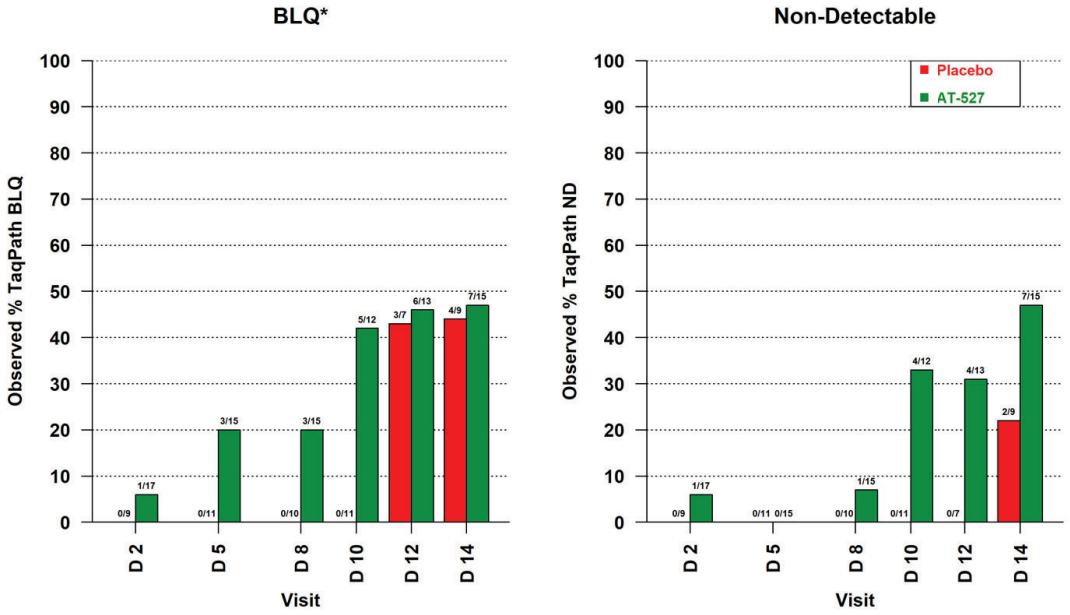
This antiviral signal was further interrogated in the subset of patients with higher baseline viral loads (VL) above the median of 5.26 log_{10} as compared to placebo (see figure below). Similarly, antiviral activity of AT-527 was also observed in this subset of patients, further suggesting a signal that warrants additional study. As the AT-527 group had lower viral loads at baseline in this sub-set of patients, an exploratory analysis with the baseline viral load threshold lowered to 5.0 log_{10} was conducted in which both treatment groups had similar mean viral loads at baseline. Results were consistent and showed a similar trend toward earlier viral clearance in the AT-527 group.

Quantitative SARS-CoV-2 RNA, mITT with Baseline VL ≥ median (5.26 log10 copies/mL)



Patients in the AT-527 arm achieved SARS-CoV-2 clearance (no detectable RNA or target not detected (TND)) as early as Day 2 (6%), Day 8 (7%) and Day 10 (33%), Day 12 (31%) compared to 0% in the placebo arm at the same timepoints. By Day 14 (last viral sampling study day) approximately 47% of patients in the AT-527 arm and 22% in the placebo arm had no detectable RNA virus (TND) (see figure below).

Qualitative SARS-CoV-2 RNA, mITT Patients with Baseline VL ≥ median (5.26 log10 copies/mL)



AT-527 dosed as 550 mg BID for 5 days was generally well-tolerated in this population. There were no drug-related SAEs. Non-serious AEs were equally distributed across treatment arms. Most were mild-to-moderate in severity and assessed as not related to the study drug. No clinically significant abnormal ECGs were reported. No safety concerns or newly determined risks were identified.

Although the Sponsor acknowledges the futility of demonstrating a treatment effect on PRI in this study, as the small number of disease progression events will not be sufficient to provide a meaningful measure of clinical effect, the Sponsor believes that the rapid and sustained antiviral activity described above warrant further evaluation in this high-risk patient population. As such, the Sponsor has decided to continue the study with a second cohort of patients receiving a higher AT-527 dosing regimen of 1100 mg BID for 5 days. The original design utilizing the 550 mg BID dose, which enrolled 81 patientswill be referred to as Part A; the second half of the study which will dose patients at 1100 mg BID will be considered Part B of the study. Part B will have a virologic primary endpoint and will explore whether higher doses result in a more pronounced antiviral effect in this population. If so, these data would further support dose selection for the program and this patient population. The 1100 mg BID dose is also being evaluated in an ongoing Phase 2 outpatient study (NCT04709835) and ongoing Phase 1 study in health volunteers (AT-03A-002).

1.2. Rationale for the Dose Selection

1.2.1. Rationale for AT-527 550 mg BID Dose Regimen in Part A

The starting dose regimen in Part A of this study was 550 mg AT-527 BID for 5 days. This regimen was supported by the following data:

- Tissue distribution data for the active triphosphate metabolite AT-9010 in non-human primate and production rates of AT-9010 in human and cynomolgus monkey hepatocytes incubated with 10 μM AT-511 (see details in the AT-527 Investigator's Brochure, Section 4.2.2.2 and Table 6-1)
- Predicted PK profiles for AT-9010 in the lung at the studied 550 mg BID regimen (see details in the AT-527 Investigator's Brochure, in Figure 6-1)

At steady state, the 550 mg BID regimen was predicted to deliver the following values:

- Mean trough AT-9010 (the active triphosphate metabolite) concentrations at 12 hours ($C_{12\ hr}$) in the lung at about 0.9 μM, 1.8-fold higher than the mean EC_{90} of 0.5 μM determined for the free base AT-511 in an in vitro antiviral activity assay in SARS-CoV-2-infected human airway epithelial cells (AT-527 Investigator's Brochure)
- Mean maximum lung AT-9010 concentrations at about 1.5 μM (time to maximum concentration at about 4 hours postdose), 3-fold higher than the mean EC_{90} of 0.5 μM.

The 550 mg BID regimen has been evaluated in the ongoing Phase I Study AT-03A-002; 20 healthy subjects (blinded, 1:1 randomization active vs. placebo) were enrolled and have completed dosing and follow-up through Day 10; no safety concerns have been identified.

Data for AT-527 550 mg once a day (QD) combined with daclatasvir 60 mg QD in HCV infected patients was also available from a completed 12-week study (AT-01B-002). In that study, most patients received a cumulative total dose of AT 527 30,800 mg (over 8 weeks). Safety and tolerability data from the study provide a safety margin of 5.6-fold for a 5-day (5500 mg cumulative dose) treatment regimen for COVID-19 patients.

The animal and human systemic exposure parameters summarized in Table 6-2 of the AT-527 Investigator's Brochure indicate that the steady-state exposures of AT-511 and its metabolites achieved at the NOAEL doses in the 13-week toxicology studies exceed or approximate unity for the AT-527 550 mg BID dose in the target population of this study.

These considerations supported an expected favorable safety profile for the evaluation of the 550 mg BID dose regimen in the target population in Part A of the study.

Based on the emerging data described in the interim analysis above as well as the favorable safety profile observed at 550 mg BID, the Sponsor is proposing a subsequent cohort (Part B) to evaluate a higher dose of 1100 mg BID for 5 days.

1.2.2. Rationale for AT-527 1100 mg BID Dose Regimen in Part B

The available nonclinical and clinical evidence supported the starting regimen of 550 mg BID. However, a higher dose regimen (1100 mg BID for 5 days) has been selected to further explore

the dose-exposure-response profile for AT-527 and delineate the relationship between plasma concentration of AT-273, a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010, and antiviral activity.

At steady state, this regimen is predicted to achieve the following values:

- Mean trough AT-9010 concentrations at 12 hours ($C_{12\,hr}$) in the lung at about 1.8 μM, 3.6-fold higher than the mean EC_{90} of 0.5 μM determined for AT-511 in the in vitro antiviral activity assay in SARS-CoV-2 infected human airway epithelial cells
- Mean maximum AT-9010 concentrations in the lung at about 3.0 μM, 6-fold higher than the mean EC_{90} of 0.5 μM

Exposure multiples for the maximum concentration (C_{max}) and the area under the concentration-time curve over the dosing interval at steady state ($AUC_{\tau,ss}$) of AT-511, AT-551, AT-229, and AT-273 in plasma at the highest planned AT 527 dose in this study (1100 mg BID) are presented in Table 1-1.

Plasma exposures achieved in the repeat-dose toxicity studies in the rat and the non-human primate either exceed or approximate the anticipated clinical exposures for the different metabolites in one or both species, depending on the metabolite, and are consistent with the International Council for Harmonisation (ICH) document on metabolite coverage including prodrug approaches (ICH 2008).

Table 1-1 Predicted Rat and Non-Human Primate Exposure Multiples for AT-511 (Free Base Form of AT-527) and Its Major Metabolites AT-551, AT-229 and AT-273 at a Human Dose of AT-527 1100 mg BID

	Monkey: Day 5 1000 mg/kg		Monkey: 13-wk 650 mg/kg		Rat: 13-wk 1000 mg/kg	
	Males	Females	Males	Females	Males	Females
C_{max}						
AT-511	1.6	1.2	2.0	1.0	0.01	0.04
AT-551	8.0	17.5	5.5	3.2	15.1	27.8
AT-229	2.1	2.0	1.0	0.8	2.0	4.3
AT-273	0.4	1.1	0.7	0.6	1.1	1.5
$AUC_{\tau,ss}$						
AT-511	2.9	1.0	1.3	1.5	0.01	0.02
AT-551	8.0	11.4	4.2	2.4	6.0	6.6
AT-229	1.6	0.9	0.6	0.7	1.7	2.8
AT-273	0.3	0.5	0.4	0.4	0.8	1.1

$AUC_{\tau,ss}$ = area under the concentration–time curve during the dosing interval at steady state; Cmax = maximum concentration.

The 1100 mg BID dose is also being evaluated in an ongoing Phase 2 outpatient study (WV43042) and ongoing Phase 1 study in health volunteers (AT-03A-002).

1.3. Study Rationale

As there are currently very limited treatment options for COVID-19, there is an unprecedented urgent need to develop new therapies. These should be agents that are proven safe and effective in controlled clinical trials. Rigorously studied agents could prove to be lifesaving for COVID-19 patients if they substantially reduce disease progression to respiratory failure. Progression of respiratory insufficiency to respiratory failure (requiring mechanical ventilation or ECMO) is often fatal for severely ill COVID-19 patients and is more common in older patients with associated risk factors. As noted above, fatality rates for COVID-19 patients who have progressed to intubated mechanical ventilation have been reported to be about 50% or higher in U.S. patients and over 80% in ex-U.S. patients.

Participants in this clinical trial represent a high-risk population with significant comorbidities associated with poor outcomes such as obesity, diabetes, asthma and hypertension. Although the risk for severe COVID-19 increases with age, recent data indicate that younger adults are also at significant risk. In the US, the median age of COVID-19 cases continues to decline from the earlier times of the epidemic, most recently from 46 years old in May 2020, to 37 years old in July 2020, and 38 years old in August 2020. Similar trends were reflected in the increased frequency of emergency room visits in younger adults. The highest incidence of COVID-19 during June through August 2020 was in 20–29 year old adults, accounting for >20% of all confirmed cases (Boehmer TK, DeVies J, Caruso E, et al. 2020). As a consequence of the declining average age of infection, there is now a significant overlap of moderate and severe COVID-19 in younger adults with risk factors. In a recent database analysis, adults age 18 to 34 years old hospitalized with COVID-19 experienced frequent adverse outcomes: 21% required intensive care, 10% required mechanical ventilation, with a 2.7% of overall mortality rate (Cunningham JW, Vaduganathan M, Claggett BL, et al. 2020). In this series, obesity, hypertension, and diabetes were associated with the worst outcomes, with younger patients with more than 1 factor having a comparable risk to older adults without them. In the US population, these risk factors are a common finding in young adults: the prevalence of obesity in the US in 2017-2018 was 40.0% among adults aged 20–39, hypertension now affects 1 in 8 adults aged between 20 and 40 years old, and approximately 13% of those > 18 years old in the US have diabetes, with 4% being between the age of 18-44 years (Hales CM, et al. 2020; Centers for Disease Control and Prevention - National Diabetes Statistics Report 2020; Hinton TC, et al. 2020). These trends have also been growing internationally with a surge in new COVID 19 cases linked to young people in multiple countries in Europe. Obesity and its associated comorbidities are also on the rise in young people in many areas of the world (World Health Organization 2017). Based on these considerations, derived from our evolving understanding of the disease, an expansion of the age criteria was warranted in order to address the emerging unmet need and to allow participation in the trial of a younger, more representative population at risk.

Urgent clinical evaluation of AT-527 in COVID-19 patients is supported by extensive non-clinical safety data, Phase 1-2 clinical safety data in healthy volunteers and HCV-infected

patients, the supportive human PK data, and the potent activity of AT-527 against SARS-CoV-2 replication. The *in vitro* virology data for AT-527 show potent inhibition of SARS-CoV-2 replication, with a mean EC_{90} concentration (0.5 µM). This is a level that can be easily achieved and continuously maintained systemically with the AT-527 dosing regimens stipulated for this study. As noted above in Section 1.1, a promising antiviral activity and safety profile at 550 mg BID in Part A was described with the interim analysis, although clinical efficacy could not be demonstrated due to the low disease progression rates. Nevertheless, with the positive antiviral signal, the Sponsor is proposing to explore a higher AT-527 dose of 1100 mg BID for 5 days to potentially optimize the antiviral activity.

In summary, AT-527 is an orally administered, well-tolerated, potent anti-RNA virus candidate recently progressing in Phase 2 studies with hepatitis C patients, which has been repurposed for evaluation in COVID-19 patients. Initial efficacy goals in Part A were to substantially reduce progression to higher levels of respiratory insufficiency and to shorten patients' acute illness, however, clinical efficacy could not be demonstrated due to the small number of patients achieving the PRI endpoint. The current trial is a randomized, double-blind, placebo-controlled clinical study to rigorously evaluate the safety and efficacy of AT-527 in hospitalized/confined adult (≥18 years of age) COVID-19 patients with moderate disease and risk factors for poor outcomes. The primary efficacy goal in Part A was to significantly reduce progressive respiratory insufficiency in this high risk population, assessed by comparing the proportions of subjects (active vs. placebo recipients), who experience a 2-tier or greater increase in required respiratory support methods, using a 6-tier scale described in Section 6.9. As the futility of demonstrating a treatment effect on PRI in this study has become apparent based on the low event rates, the primary endpoint for Part B will be changed to a virologic endpoint.

AT-527 (or placebo) will be administered along with supportive local standard of care (SOC) therapy per local/institutional practices or guidelines, with the exception of antiviral drugs with activity against SARS-CoV-2. Supportive SOC will not be dictated by the protocol. Placebo plus SOC control groups will be utilized to assess whether AT-527 can demonstrate clinical/antiviral benefit over currently available SOC. Treatment-assignments (active vs. placebo) will be randomized and double-blind. Positive data from this study could potentially support subsequent outpatient studies in patients with milder disease as well as controlled studies of early-treatment of asymptomatic or minimally symptomatic SARS-CoV-2 positive persons, and controlled prophylaxis studies in important risk populations (e.g. close contacts of COVID-19 patients, healthcare workers and first responders). An orally administered SARS-CoV-2 direct-acting antiviral which demonstrates safety and clinical benefit in COVID-19 patients would have important impact on ameliorating illnesses in the current crisis, and could be life-saving if treatment is found to reduce patients' disease progression.

1.4. Risk/Benefit Assessment

The extensive non-clinical data and clinical data from HCV patients summarized above and in the AT-527 Investigator's Brochure indicate an encouraging risk-benefit expectation for AT-527 treatment of COVID-19 patents, supporting program advancement to the present Phase 2 clinical trial with an expectation of satisfactory clinical safety and appreciable antiviral activity. Non-clinical and clinical safety studies have not revealed any pattern of drug-attributable clinical adverse effects or any consistent clinically significant laboratory abnormalities related to any body system. Total daily doses in this COVID-19 study are higher than evaluated in the HCV

program; however, the 5-day cumulative AT-527 dosing exposure for COVID-19 subjects is much less than the cumulative AT-527 exposures in the HCV program (8-12 weeks). Based on cumulative total dose received in the HCV program (30,800 mg for most subjects), there is a safety margin of 5.6-fold for the 5-day 550 mg BID COVID-19 treatment regimen (5,500 mg cumulative dose) and a 2.8-fold margin for the 1100 mg BID (11,000 mg cumulative dose) treatment regimen.

While *in vitro* data are consistent with AT-527 having a low potential for mitochondrial toxicity, some nucleoside analogues have been associated with this toxicity, resulting in damage to liver, muscles, heart, nerve, pancreas and other organs. Nephrotoxicity has also been associated with the use of some nucleoside analogs (e.g. tenofovir), but is not a class effect. The completed non-clinical assessments of AT-527 suggested negligible potential for mitochondrial toxicity. The active triphosphate of AT-527 did not inhibit the *in vitro* enzyme activities of human cellular DNA-dependent DNA polymerases (α, β or γ) and was poorly incorporated by human mitochondrial RNA polymerase (POLRMT), with a low efficiency that was similar to that of the triphosphate of sofosbuvir, a nucleoside analog that has been quite safe in broad use in HCV patients. Additionally, neither AT-527 nor sofosbuvir had any effect on mitochondrial integrity using cell-based assays. To date, there have been no clinical signs of adverse events (AEs) suggesting mitochondrial toxicity for AT-527 dosing, in animal toxicology studies or the clinical studies.

The present protocol mandates thorough clinical and laboratory safety monitoring, with routine frequent testing of the following parameters: liver function tests (including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and alkaline phosphatase), creatine kinase (CK) and isoenzyme levels, electrocardiogram (ECG) monitoring and renal function parameters (including serum creatinine and blood urea nitrogen (BUN)). Standard serum chemistries, complete blood counts (CBC) with differentials, urinalyses and clinical AEs will also be monitored. Current medically used nucleoside analogs are primarily renally cleared, but dose adjustments are generally not needed for patients with creatinine clearance values ≥ 60 mL/min. With this perspective, the present protocol excludes patients with creatinine clearance < 60 mL/min

Although it is reasonable to expect that a SARS-CoV-2 direct-acting antiviral with potent (sub-micromolar) *in vitro* antiviral activity will result in clinical benefit, AT-527 is still currently being tested in clinical trials in COVID-19 patients. Thus, it is possible that subjects will not receive any benefit from participation in this study. As noted, an independent DSMB has been established to periodically assess safety and potential risk/benefit, as described in Section 3.1 and Section 10.1.

The likelihood of substantial antiviral efficacy in these subjects is supported by the favourable human PK profile observed in human volunteers and HCV patients, which is predicted to be sufficient for achieving and maintaining systemic AT-527 concentrations above the SARS-CoV-2 EC_{90}.

The non-clinical and clinical data for AT-527 summarized in this protocol therefore support the probability of a favourable benefit-risk profile for AT-527 in the treatment of COVID-19 patients.

2. STUDY OBJECTIVES

The objectives of this study are to evaluate the safety, antiviral activity, tolerability and efficacy of AT-527 in adult subjects (≥18 years of age) with moderate COVID-19 and risk factors for poor outcomes.

The primary efficacy goal for Part A (secondary for Part B) is to significantly reduce PRI, assessed with the 6-tier scale of increasing levels of respiratory support described in Section 6.9. The most important potential treatment benefit is significantly reducing subjects' PRI, which will be assessed as the proportions of subjects experiencing a 2-tier or greater need in respiratory methods, with a goal to reduce such progressions by 50% in active-treated subjects vs. placebo recipients.

The primary efficacy goal for Part B (secondary for Part A) is to provide greater reduction in SARS-CoV-2 virus RNA as measured by RT-PCR at specified timepoints.

Secondary efficacy goals include: shortening in median time to clinical recovery by at least 4 days (based on achieving disease resolution in the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Status scale); reduction in progression to respiratory failure or death, using the 6-point scale; improvement in overall Clinical Status using the NIAID ordinal scale, reduction in all-cause mortality, shortening of duration of hospitalization for COVID-19, shortening of time to sustained non-detectable SARS-CoV-2 and reduction in proportion of subjects SARS-CoV-2 positive at Days 5 and 14.

As an exploratory objective, plasma concentrations of AT-527 and metabolites will be monitored in sparse samples collected from subjects with COVID-19.

3. STUDY DESIGN

3.1. General Study Design

This is a phase 2 double-blind, placebo-controlled, randomized treatment study evaluating AT-527 (or placebo) for 5 days in combination with supportive SOC compared to SOC alone in hospitalized/confined subjects with moderate COVID-19 disease and risk factors for poor outcomes. The study will enroll adults, ≥18 years of age, with moderate COVID-19, not on a ventilator. Subjects must also have at least one of the known common risk factors for poor outcomes: obesity (BMI>30), hypertension, diabetes or asthma. Subjects will be documented as SARS-CoV-2 positive in an assay granted EUA by the U.S. FDA.

Moderate disease will be defined by the following:

- Symptoms of COVID-19, with initial symptom onset within 5 days prior to Screening:
    - At least 1 of the following: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
- Clinical signs indicative of COVID-19 (as above), with:
    - SpO2 ≥ 93% on room air or requires ≤ 2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥ 93%

The study will be conducted in 2 Parts. Part A will evaluate an AT-527 dose of 550 mg BID for 5 days and Part B will evaluate a dose of 1100 mg BID for 5 days. Based on the interim analysis conducted after Part A (which demonstrated a positive antiviral signal but low disease progression rates in the population), Part B was added via an amendment with a virologic primary endpoint.

Part A subjects will be randomized 1:1 (active:placebo). Subjects will receive one (1) tablet of 550 mg active drug (or matching placebo) every ~12 hours to complete 5 days of treatment.

Table 3-1 Study Design

Disease Severity	Treatment Duration	Dosing Arms	
Moderate	5 days	active	550 mg AT-527 administered every ~12 hours (10 doses) + SOC
		placebo	AT-527 placebo administered every ~12 hours (10 doses) + SOC

*Randomized 1:1 (active:placebo)

- In Part A, a cohort of 20 subjects was initially enrolled to preliminarily assess the safety of the 550 mg BID dosing regimen. Enrollment was paused after the first 20 subjects, until the DSMB conducted a safety review. Upon DSMB review, a second cohort of 20 subjects was enrolled in Part A and enrollment was paused until the DSMB conducted a safety review of these data. Again, the DSMB allowed the study to continue without modification.
- In order to perform the interim analysis, Part A enrollment was paused by the Sponsor after 81 subjects were randomized. As described in Section 1.1, no additional subjects will be randomized in Part A with implementation of Amendment 8.
- Part B subjects will be randomized (1:1) to one of the two following arms:

Disease Severity	Treatment Duration	Dosing Arms	
Moderate	5 days	active	1100 mg AT-527 administered every ~12 hours (10 doses) + SOC
		placebo	AT-527 placebo administered every ~12 hours (10 doses) + SOC

*Randomized 1:1 (active:placebo)

- Up to an additional 110 subjects will be enrolled in Part B.
- An additional DSMB safety review will occur when 50% of the Part B subjects have been enrolled.

For each interim safety review, pooled safety data will be reviewed by the DSMB. The DSMB will alert the Sponsor if there are any safety concerns for active-treated subjects compared to placebo recipients.

3.2. Number of Subjects

- The study is planned to enroll 190 subjects with moderate COVID-19 and risk factors for poor outcomes; determination of the targeted sample size is described in Section 8.2.
    - Part A: 81 subjects were randomized at the time of the Part A interim analysis.
    - Part B: Up to an additional 110 subjects will be enrolled in Part B.

4. SUBJECT SELECTION

4.1. Study Population

Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for participation in this study.

4.2. Inclusion Criteria

1. Willing and able to provide informed consent.
2. Male or female subjects ≥18 years of age.
3. Subject is hospitalized or in a hospital-affiliated confinement facility for which the principal investigator is credentialed and study staff have access to study participants and their data.
4. Subject must be diagnosed with COVID-19 (SARS-CoV-2 positive) by a standard assay or equivalent testing. *Note: SARS-CoV-2 infection will be confirmed with an FDA EUA-approved assay.*
5. Moderate disease defined by the following:
    - Symptoms of COVID-19, with initial symptom onset within 5 days prior to Screening:
        - At least 1 of the following: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
    - Clinical signs indicative of COVID-19 (as above), with:
        - SpO2 ≥ 93% on room air or requires ≤ 2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥ 93%
6. Subjects must also have at least one of the following known risk factors for poor outcomes: obesity (BMI>30), hypertension, diabetes or asthma.
7. QTcF interval ≤ 450 ms for males and ≤ 460 ms for females at Screening.
8. Females of childbearing potential must agree to use protocol specified methods of contraception as described in Section 5.9.
9. Females of childbearing potential must have a negative pregnancy test at Screening.
10. Subject must be able to take oral tablet medications.

11. Subject is, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements.

4.3. Exclusion Criteria

1. Female subject is pregnant or breastfeeding.
2. Clinical signs indicative of severe or critical COVID-19 illness, defined as any of the following: RR ≥30, HR ≥125, SpO2 <93% on room air or requires >2L/min oxygen by nasal cannula or mask to maintain SpO2 ≥93%, systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg or PaO2/FiO2 <300
3. Any subject with a concomitant life-threatening condition, including but not limited to the following: requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), acute respiratory distress syndrome (ARDS), shock, cardiac failure or suspected bacterial sepsis.
4. Evidence of lobar or segmental consolidation on chest imaging.
5. Congestive heart failure or myocardial infarction within the previous 6 months.
6. Recurrent nausea, vomiting or known malabsorption syndrome, that would interfere with oral medication treatment.
7. Creatinine clearance < 60 mL/min (Cockcroft-Gault formula)
8. Abuse of drugs or alcohol that could interfere with adherence to study requirements as judged by the investigator.
9. Treatment with other drugs thought to possibly have activity against SARS-CoV-2.
   Note: If the subject was previously treated with such an agent, treatment must have been discontinued at least 7 days prior to planned dosing on the current trial. The use of hydroxychloroquine is not allowed in this trial. Convalescent plasma is permitted as part of local SOC.
10. Use of other investigational drugs within 30 days of dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study.
11. S-T segment elevation or other clinically significant abnormal ECG at Screening, as determined by the investigator.
12. Subject has a history of active hepatitis B infection or uncured hepatitis C infection. Subjects with human immunodeficiency virus (HIV) infection are allowed, as long as they are virologically suppressed with CD4 count at least 500 cells/mm^3.
13. Active clinically significant diseases including:
    - Active urinary tract infection
    - History of severe renal impairment or receiving renal replacement therapy (hemodialysis, peritoneal dialysis)
14. Subjects with malignant disease can continue antineoplastic therapy during the study period *unless* the antineoplastic therapy includes an immunomodulator or is expected to result in severe bone marrow suppression during the study (e.g., risk for grade 3 or higher anemia, leukopenia, or thrombocytopenia).

15. Requires use of immunosuppressive doses of systemic corticosteroids, defined as the equivalent of 20 mg prednisone daily during any two week time period (280 mg prednisone equivalent total dose) in the three months prior to study entry. Standard of care dexamethasone indication and dosing are permitted if needed for treatment of COVID-19 Syndrome.
16. Requires use of immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions) during the primary 14-day study period.
17. Requirement of any prohibited medications (Section 5.8).
18. Abnormal values at Screening:
    - ALT or AST > 5 x upper limit of normal (ULN)
    - Total bilirubin > 1.5 x ULN, unless the subject has known Gilbert's syndrome
    - Hemoglobin < 10 g/dL for females or < 12 g/dL for males
    - Total white blood cell (WBC) count < 2,500/mm^3 or absolute neutrophil count < 800/mm^3
    - Platelet count < 80 x 10^9/L
19. Any clinically significant medical condition or laboratory abnormality that, in the opinion of the investigator, could jeopardize the safety of the subject or impact subject compliance or safety/efficacy observations in the study.
20. Has received or is expected to receive any dose of a SARS-CoV-2 vaccine before the Day 14 visit.

One-time retests of individual Screening laboratory parameters or assessments may be permitted in certain scenarios. Such scenarios may include lab processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting Screening laboratory results.

5. STUDY TREATMENTS

5.1. Description and Handling of Study Treatments

5.1.1. Test Product

AT-527 will be provided by the Sponsor as 550 mg tablets.

5.1.2. Control Product(s)

Matching placebo tablets for AT-527 will also be provided by the Sponsor.

AT-527 (or placebo) will be administered along with local supportive SOC therapy per local/institutional practices or guidelines. Other than restrictions listed in Section 5.8, SOC will not be dictated by the protocol.

5.1.3. Packaging and Labeling

The Sponsor will be responsible for ensuring that study drugs (active and placebo) are manufactured in accordance with applicable Good Manufacturing Practice regulations and requirements. The labels for the study drug(s) will meet applicable local regulatory requirements.

5.1.4. Storage and Handling

Study drugs should be stored under the conditions described on the label.

5.2. Method of Assigning Subjects to Treatment Groups

A unique subject number will be assigned to each subject at Screening. Once assigned, it will not be reassigned to another subject. Once eligibility is confirmed, subjects will then be randomly assigned to a treatment group (active vs. placebo) according to a randomization list, generated by the designated independent biostatistician. This will be through a centralized randomization process and eligible subjects may also receive a unique randomization number linked to a treatment assignment.

5.3. Blinding

Treatment assignments will be blinded to the investigator, research staff, subjects, CRO and Sponsor for the entire study, unless unblinding is mandated by a DSMB recommendation. The study blind will be broken upon completion of the clinical study and after the study database has been locked. The only exceptions will be those described with the DSMB analyses and procedures (Section 10.1).

During the study, the blind may be broken for an individual subject by the investigator only in emergencies or when knowledge of a subject's treatment group is necessary for further subject management. Although not necessary in the case of an emergency, the investigator should discuss the specific case with the Sponsor prior to unblinding. The date and reason for breaking the blind must be recorded.

As noted in Section 10.1. the Sponsor, CRO, and clinical site personnel will remain treatment-blinded to the data reviews by the DSMB, unless the DSMB promulgates a study guidance recommending study halt for efficacy, safety, or futility.

5.4. Dosing and Administration

5.4.1. Dispensing

Based on their randomization assignment, blinded study drug (active or placebo) will be assigned depending on treatment arm. Designated site staff will dispense the blinded study drugs (active or placebo) to each subject at each dispensing day/time. The date and time of each dose must be recorded. If subjects are discharged from the hospital prior to study drug completion, they will be provided with study drug to be taken at home to complete their assigned treatment course.

5.4.2. Administration Instructions

Part A

Subjects will take one (1) tablet (550 mg AT-527 or placebo x 1) administered approximately every 12 hours (i.e. BID) for the 5-day treatment period.

Part B

Subjects will take two (2) tablets (550 mg AT-527 or placebo x 2) administered approximately every 12 hours (i.e. BID) for the 5-day treatment period.

Study drugs will be taken orally and should be taken at approximately the same time each day, ideally within an approximate 2 hour window (as a guidance). The drugs may be given with water. Previous studies indicate no appreciable effect of food on AT-527 absorption, so study dosing can be done between or during mealtimes. Regular daily timing is preferred, to consistently achieve dose intervals of approximately 12 hours. Dosing on Day 1 can occur at any time of day (AM or PM).

If a dose is missed, subjects should be instructed to take the missed dose(s) of study drugs as soon as possible during the same day. Subjects should never double the next dose with a missed dose.

5.4.3. Treatment Compliance

Doses will be administered under the supervision of designated site staff to ensure treatment compliance.

If subjects are discharged from the hospital prior to study drug completion, they will be provided with study drug to be taken at home to complete their assigned treatment course, and compliance will be confirmed by follow-up telephone call or potentially an at-home visits by trained medical professional(s) (if feasible).

5.5. Study Drug Accountability

Complete and accurate records of all study drugs must be kept. These include acknowledgment of receipt of each shipment of study product, subject dispensing records and returned or destroyed study product.

At the end of the study, all unused study drugs and containers will be returned to the Sponsor (or designee) or destroyed, per the instruction of the Sponsor. Documentation confirming drug accountability will be reviewed over the course of the trial.

5.6. Stopping Rules

5.6.1. Safety Stopping Rules for Individual Subjects

Treatment will be discontinued in any subject who experiences any one of the following:

- progression to requirement for mechanical ventilation or ECMO
    - Note: For any subject who progresses to mechanical ventilation or ECMO, study treatment should be discontinued, as there is no IV form of the study drug. The subject may then receive any other available treatments, with

continued study observation for post-treatment safety data to hospital discharge or death as locally feasible. Subjects who have completed or discontinued study drug may be treated with any other available therapeutic agent, as locally allowed. If the agent is investigational it should be an agent that has institutional Ethics Committee or Research Committee approval, or FDA EUA.

- confirmed elevation of ALT or AST > 3 x baseline with direct bilirubin > 2 x ULN or INR increased from baseline and > 1.5 x ULN, without evident alternative cause for these elevations
- confirmed new onset ≥ grade 3 serum creatinine (> 1.8 x ULN and > 2 x baseline), or decreased creatinine clearance to < 60 mL/min
- any SAE, or a grade 4 AE or clinically significant confirmed grade 4 laboratory abnormality for an individual subject which is considered by the investigator to have a reasonable possibility of relatedness to study drug
    - Note: To warrant treatment discontinuation for a study subject, a **confirmed grade 4 laboratory abnormality should have clinically significant findings** expected to be associated with the laboratory abnormality. Subjects with isolated asymptomatic laboratory abnormalities, without any clinical correlations, are allowed to remain on treatment with continued monitoring according to the preference of the investigator. Also, subjective clinical symptoms not reflecting major organ dysfunction, such as severe headache, may or may not warrant treatment discontinuation in the judgement of the investigator.
- Pregnancy

A confirmed value is defined as one that is found to have a similar value at the next subsequent test. Any of the above laboratory results and all ≥ grade 3 new onset laboratory abnormalities must be repeated as soon as possible, preferably within 24 hours upon reporting of the initial value. If a grade 3/4 lab abnormality is determined to be clinically significant, it should be reported as an AE and should include an assessment of causality. Definitions of clinical significance of laboratory abnormalities are summarized in Section 7.1.1. For any grade 3/4 AE or laboratory abnormalities, the site must enter the data into the Electronic Data Capture (EDC) system within 24 hours.

Subjects who prematurely discontinue study treatment should complete early termination (ET) assessments at the time of treatment discontinuation, as described in Table 6-1. However, these subjects should be encouraged to remain in the study and maintain the same protocol schedule and assessments as described in Table 6-1. This will allow for continued follow-up for key study outcome data.

5.6.2. Study Stopping Rules

COVID-19 is a protean, sometimes fatal, illness for which the spectrum of disease-related signs and symptoms is still being delineated. Aside from principal involvement of the respiratory tract, with potentially severe pneumonia, it is increasingly clear that clinical manifestations can also include multi-organ manifestations due to a hyper-coagulopathy with widespread thromboembolic processes in other body organs - liver, heart, brain, etc. With this perspective, a

multi-organ variety of clinical AEs and laboratory abnormalities can be expected from COVID-19 study populations, regardless of treatment. Effective therapies may reduce COVID-19 disease manifestations over time, but the wide variety of COVID-19 related AEs and laboratory abnormalities will be seen in both active- and placebo-treated subjects until therapy mitigates the disease or the disease spontaneously resolves.

This clinical trial will be paused for a DSMB review of safety data, for any of the following reasons:

- Death in any subject in which the cause of death is judged to have a reasonable possibility of relatedness to the study drug by the investigator.
- The occurrence in any subject of a life-threatening SAE whose causal relationship is judged to have a reasonable possibility of relatedness by the investigator.
- >20% of the enrolled subjects experience clinically significant grade 3/4 AEs or clinically significant confirmed grade 3/4 laboratory abnormalities considered by the investigator to have a reasonable possibility of relatedness to the study drug.

Additional rules will be applied for the first two enrolling cohorts of 20 subjects each in Part A. For each 20-subject cohort, the study will also be paused for a DSMB safety review for any of the following reasons:

- Two (2) occurrences of grade 3 or higher clinical AEs that are assessed to have a reasonable possibility of relatedness to the study drug by the investigator.
- Two (2) occurrences of a clinically significant grade 3 or higher laboratory abnormality assessed to have a reasonable possibility of relatedness to the study drug by the investigator.

For any of the above circumstances, a pause in further study enrollment will be triggered. The DSMB will then review unblinded safety data for the referenced events, to determine if active treatment poses an appreciably greater risk for these events or other concerning safety events compared to placebo treatment. If the latter appears to be the case, the Sponsor will collect and review all the available safety data with the DSMB, clinical investigators, and regulatory authorities (including US FDA), to obtain an overall risk assessment for active vs. placebo treatment, and agreement on a plan forward.

Collaborative decisions on study stoppage will include consideration of the relative occurrence of the given AE or lab abnormality in active- vs. placebo-treated subjects, and the clinical severity of the specific AE or lab abnormality. For example, in consideration of the severity gradations in the Division of AIDS (DAIDS) table, transient episodes of grade 3-4 headaches, anorexia, fatigue/malaise, myalgias/arthralgias, psychologic manifestations, and other AEs and lab abnormalities in the DAIDS table, are likely to be observed with placebo recipients and active-treated subjects in this clinical trial; and early datasets could by chance show more events for active-dosed subjects vs. placebo recipients. In those circumstances an agreed plan for further study conduct will be achieved by a collaborative safety review involving the Sponsor, DSMB, clinical investigators, and regulatory authorities (including US FDA).

In addition, this study could be stopped by a DSMB recommendation for study stoppage due to efficacy, safety, or futility as described in Section 10.1.

5.7. Premature Treatment or Study Discontinuation

Subjects may voluntarily discontinue treatment or withdraw from the study at any time. They may also be removed from the study at the discretion of the investigator or Sponsor at any time. The investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject.

Premature treatment discontinuation may occur for any of the following reasons:

- Persistent noncompliance with the protocol requirements
- Pregnancy
- Adverse event precluding further study participation due to safety concerns or compliance issues
- Subject request
- Investigator request
- Sponsor request

Subjects who prematurely discontinue study treatment should complete Early Termination (ET) assessments at the time of treatment discontinuation, as described in Table 6-1. However, subjects who prematurely discontinue treatment should be encouraged to remain in the study and maintain the same protocol schedule and assessments as described in Table 6-1. This will allow for continued follow-up for key outcomes.

The end of the study for any individual subject will be defined as the 49-day follow-up visit.

5.8. Prior and Concomitant Medication

Continuation of subject's maintenance medications is allowed - e.g. medications for treatment of hypertension, high cholesterol, anti-coagulation prophylaxis, asthma, diabetes, HIV, musculoskeletal disorders, cardiac arrhythmias, anxiety disorders, medication-controlled psychosis, etc. Concomitant medications will be documented in the study case records. If there are questions regarding concomitant medications for individual subjects, the Investigator or a site team member should contact their CRO site monitor.

As convalescent plasma may be considered standard of care in some regions, it's concomitant use is allowed in this study.

5.8.1. Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Hormonal contraceptives
- Acetaminophen *(paracetamol)*
- Hormone replacement therapy
- Prescribed medications for concomitant conditions as per medical history

- Low dose aspirin

5.8.2. Cautionary Therapy

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions *(DDI)* are generally unknown.

In *vitro* experiments, AT--511 (the free base form of AT-527) demonstrated the potential for *the following DDIs (see Appendix 2 for more details)*:

P-glycoprotein (P-gp)

AT-511 is a substrate and an inhibitor of P-gp.

- *P-gp inhibition: staggered dosing can effectively mitigate potential for a clinical DDI at the level of the gastrointestinal tract. In the event that sensitive substrates of P--gp with a NTI cannot be safely discontinued or substituted, they should be dosed 2 hours after study drug administration, by which time absorption of AT-511 is considered essentially complete. Common examples of P-gp sensitive substrates with NTI include digoxin and tamoxifen.*

  For a list of sensitive P-gp substrates with NTI refer to https://go.drugbank.com/categories/DBCAT004027.

- Use of P-gp inhibitors (other than hydroxychloroquine or amiodarone; see Prohibited Therapy section below) may be permitted by staggering the dosing of *study drug* and the P-gp inhibitor by 2 hours (with *study drug* dosed first).

  For a list of P-gp inhibitors, refer to https://go.drugbank.com/categories/DBCAT002667

  Macrolides (including azithromycin) may be used if dosing is staggered as described above.

Breast Cancer Resistance Protein (BCRP) sensitive substrates

AT-511 is an inhibitor of BCRP.

- *BCRP inhibition: staggered dosing can effectively mitigate potential for a clinical DDI. In the event that sensitive substrates of BCRP with NTI cannot be safely discontinued or substituted, they should be dosed 2 hours after study drug administration. Common examples of BCRP sensitive substrates include ivermectin, pravastatin, rosuvastatin, apixaban and rivaroxaban.*

  For a list of sensitive BCRP substrates refer to https://go.drugbank.com/categories/DBCAT002663.

Organic Anion Transporter 1 and 3 (OAT1 and OAT3) inhibitors

The plasma circulating nucleoside metabolite AT-273 (inactive metabolite of AT-511) is a substrate of OAT1 and 3 (See Appendix 2 for more details).

- *OAT1 and OAT3 inhibitors may affect plasma levels of AT-273. However, AT-273 is considered an inactive metabolite, and changes in AT-273 PK are not expected to affect the antiviral activity of AT-527. Consider stopping drugs that are major OAT1/3 inhibitors during study treatment and resume 12 hours after the final dose of study drug. In the event that the OAT1/3 inhibitors cannot be safely discontinued or substituted, they should be used with caution. Common examples of OAT1/3 inhibitors include furosemide, losartan and cimetidine.*

For a list of OAT1 and OAT3 inhibitors, refer to https://go.drugbank.com/categories/DBCAT004041 and https://go.drugbank.com/categories/DBCAT003946, respectively.

5.8.3. Prohibited Therapy

Use of the following concomitant therapies is prohibited from Day 1 (unless otherwise specified below) until study completion or early termination, as described below:

- Treatment with other drugs thought to possibly have activity against SARS-CoV-2

  Note: If the subject was previously treated with such an agent, treatment must have been discontinued at least 7 days prior to planned dosing on the current trial. The use of hydroxychloroquine is not allowed in this trial.
- Other investigational drugs within 30 days of dosing.
- Subjects with malignant disease can continue antineoplastic therapy during the study period unless the antineoplastic therapy includes an immunomodulator or is expected to result in severe bone marrow suppression during the study (e.g., risk for grade 3 or higher anemia, leukopenia, or thrombocytopenia).
- Use of immunosuppressive doses of systemic corticosteroids, defined for this study as the equivalent of 20 mg prednisone daily during any two week time period (280 mg prednisone equivalent total dose) in the three months prior to study entry. Standard of care dexamethasone indication and dosing are permitted if needed for treatment of COVID-19 Syndrome.
- Use of immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions) during the primary 14-day study period.
- Sofosbuvir, for patients with active HCV
- Abacavir for patients with HIV
- P-gp inhibitors hydroxychloroquine or amiodarone within *3 months* prior to screening and during the study

  Use of other P-gp inhibitors may be permitted by staggering the dosing of *study drug* and the P-gp inhibitor (as described in the Cautionary Therapy Section above).

5.9. Other Study-Specific Restrictions and Requirements

- Female subjects of childbearing potential must agree to use one of the following methods of birth control from Screening through 30 days after the last dose of the study drugs:

- intrauterine device (IUD)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence*
- hormonal contraception (including combined, progesterone only or intrauterine hormone-releasing system (IUS)) together with a barrier method such as (i) male or female condom with or without spermicide or (ii) cap, diaphragm or sponge with spermicide

Note: A female subject of non-childbearing potential is defined as a female ≥ 54 years old with menses cessation for ≥ 12 months since previous menses, or a female of any age who had a hysterectomy, bilateral oophorectomy or bilateral tubal ligation.

* The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Should acceptable methods of birth control be more restrictive per local regulations, guidance or investigator practice than the methods listed above, a more restrictive list may be included within the site/country-specific Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form (ICF).

6. STUDY PROCEDURES AND GUIDELINES

Study-specific assessments and the study schedule are summarized in Table 6-1. An "X" indicates when the assessments are to be performed.

Due to COVID-19 restrictions/policies/quarantines and to maintain safety of staff at individual sites and for individual subjects, it is acknowledged that strict adherence to Table 6-1 for those procedures requiring direct contact with patients (such as laboratory sampling, physical examination, etc) may not be possible for every timepoint listed. The sites should try to maintain the schedule as closely and as safely as feasible, but temporal divergence for these direct contact procedures will not be considered a protocol deviation.

Hospital discharge may occur at any point. The date and time for the hospital discharge decision should be documented in the study records, as duration of hospitalization is a secondary study endpoint.

For subjects who are discharged before Day 14, assessments through Day 14 may be collected, either through at-home visits by trained medical professional(s), outpatient visits or by telephone follow-up, as feasible depending on the site and subject limitations.

If a subject is discharged before dosing is complete, the discharge plan should include completion of study drug dosing.

Follow-up evaluations will occur at 7 days, 14 days and 49 days after study completion at nominal Day 14, according to the table below.

Additional logistical considerations and clarifications

- It is logistically feasible and acceptable for Screening and Day 1 to occur on the same day, as long as eligibility is confirmed before dosing is initiated. If the Screening and Day 1 visits are on the same day, duplicate assessments and laboratory samples do not need to be collected twice.
- Once subjects are confirmed eligible at Screening, randomization and dosing should be initiated within 24 hrs.
- It is possible that historical laboratory results obtained as part of the subjects' standard of care prior to consenting into the current study could be used to confirm eligibility. This is acceptable as long as the samples were collected per routine standard of care, and no study-specific procedures were conducted prior to obtaining consent for the current study. However, qualifying historical laboratory results used for safety assessments must be available at Screening, and they must have been obtained within 48 hours prior to **planned dosing** from the same local laboratory to be used during the study.
- Samples collected for D-dimer levels, stored serum/plasma and PK are for future exploratory analyses only. If collection or processing of these exploratory samples impact site logistics (considering COVID-19 blood processing restrictions/limitations) or delay the ability to start study drug treatment as soon as possible for eligible subjects, collection of these exploratory samples can be skipped. This will not be considered a protocol deviation. If the site uses D-dimer levels for patient management, separate D-dimer levels can be obtained locally as available, at investigator preference per their local standard of care.
- It is recognized that some hospitalized subjects may have recovered sufficiently to not require further close medical care for their COVID-19 illness, but may be retained in the hospital/site for quarantining purposes or with consideration that the subject may be a medically or cognitively fragile individual without available family or caregiver support in their home residence, a situation which requires time for arrangement of outpatient social services support. These hospitalized subject circumstances correspond to category 6 on the NIAID ordinal scale of overall Clinical Status ("Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care for COVID-19", described in Section 6.9.).
- All subjects who prematurely discontinue study treatment should complete early termination (ET) assessments at the time of treatment discontinuation. However, these subjects should be encouraged to remain in the study and maintain the same protocol schedule and assessments as described in Table 6-1. This will allow for continued subject follow-up for key outcome data.

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Table 6-1 Schedule of Assessments

STUDY DAY(D)⇒ EVENTS⇓	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13	14	ET[e]	7, 14 and 49-day follow-up after Day 14[f]
Informed Consent	X																
Randomization	Prior to dosing																
Dosing		X[m]	X	X	X	X											
Determine Eligibility	X																
Medical History	X																
Demographics	X																
Complete Physical Examination	X					X											
Symptom-targeted Examination for AE evaluation, when needed		X[a]	X	X	X		X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X	
AEs + Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin A1c	X																
Vital signs	X	X[a]	X	X	X	X	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X	
Height (screen only)[b] and Weight	X					X											
ECG monitoring[j]	X	X[a]	X		X	X	X		X		X		X		X	X	
Safety Labs	X	X[a]	X			X			X		X				X	X	
Urinalysis	X					X											
D-Dimer, and stored samples for future analyses		X[a]	X			X			X[i]						X[i]	X	
SARS-CoV-2 Test	X	X[a,g]	X[n]	X[o]		X			X		X		X		X	X[g]	X[g]
Pregnancy Test[c]	X																
Pulse Oximetry[k]	X	X[a]	X	X	X	X	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X	
Chest Imaging[l]	X																
Ordinal scales/Clinical course data collection[h]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma samples collected for sparse PK[d]		X	X			X					X						

a) Prior to the first dose b) Height at Screening only. c) For females of childbearing potential: serum pregnancy test at Screening. d) Collected at same time as safety lab draw. e) ET=Early Termination f) As quarantine and other factors may limit the subject's ability to return to the clinic, the follow-up assessments may be conducted by telephone, video platform or at-home visits by trained medical professional(s) (with a ± 2 day window). If this follow-up is done by telemedicine, no SARS-CoV-2 samples will be collected. g) Optional h) See Section 6.9 for details of assessments, including ordinal scales for overall Clinical Status and Respiratory Support. i) Not necessary if subject already discharged from hospital j) After discharge, cardiac ECG parameters will be collected on outpatients. k) After discharge, pulse oximetry to be done on Days 2-6,8,10,12, and 14, or more frequently as needed if SpO2 < 93% l) Chest imaging (chest x-ray, CT scan, etc.) will be obtained ideally at Screening but can occur within 48 hours before screening as long as the clinical status of the subject has not changed, in the opinion of the investigator. m) Dosing on Day 1 can occur at any time of day (AM or PM). n) Collect prior to the 3rd dose (on Day 2). o) Collect prior to the 5th dose (on Day 3).

6.1. Medical History

Complete medical history will be obtained at Screening. Information about COVID-19 disease history, including the onset date of symptoms, and risk factors will be collected. Subjects may be questioned about alcohol and drug use, and information about prior or concomitant medications will also be collected.

6.2. Physical Examination

A complete physical examination will be performed by a medically qualified individual as scheduled in Table 6-1. The complete physical examination will include a review of the following: head and neck, ears/nose/throat, lymph nodes, heart, lungs, abdomen, musculoskeletal, neurological, skin and general appearance.

Demographic data (age, gender, ethnicity/race, body weight, height, body mass index (BMI)) will be recorded.

On study days which may not require a complete physical examination, a symptom-targeted physical exam should be done when needed for AE evaluation, as medically indicated.

6.3. Vital Signs

Vital sign measurements (body temperature, pulse rate, respiratory rate and blood pressure) should be captured as specified in Table 6-1. Vital signs should be assessed after subjects have had at least 3 minutes of rest and may be taken via digital vital sign monitoring.

6.4. Electrocardiogram Monitoring

ECG monitoring will be performed per hospital or intensive care unit procedures, with at least one timepoint captured for the study analysis, as specified in Table 6-1.

If logistically feasible considering COVID-19 institutional restrictions and limitations, the Screening assessment should be done using a twelve-lead ECG.

6.5. Laboratory Evaluations

Laboratory evaluations will be performed as scheduled in Table 6-1. The investigator or designee will assess each abnormal value to determine if it is clinically significant.

- Chemistry: Sodium, calcium (ionized or total calcium is acceptable per local standard of care), potassium, chloride, magnesium, bicarbonate, glucose, BUN, creatinine, creatinine clearance (Cockcroft-Gault formula), total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, albumin, CK (elevation may trigger CK isoenzyme analysis), triglycerides, cholesterol, amylase and lipase
- Hematology: WBC count with differential, red blood cell count, hemoglobin, hematocrit, reticulocyte count, mean corpuscular volume (MCV) and platelet count
- Hemoglobin A1c (glycated hemoglobin; at Screening only)
- Coagulation: Prothrombin time (PT) and INR; Note: Depending on logistics, the laboratory may use the PT to calculate INR and only report the INR to the clinical sites.

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- Troponin, N-terminal pro b-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP)
- Urinalysis: Color, appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination may be performed if the urinalysis is abnormal.
- Pregnancy tests (serum or urine) will be performed on female subjects of childbearing potential as specified in Table 6-1.

The total volume of blood withdrawn during the course of the study should not exceed 500 mL. However, it is possible that the total blood donation may be higher if repeat blood samples are required for safety assessments.

6.6. COVID-Specific Tests

Diagnostics and SOC treatment of COVID-19 are constantly evolving. The current protocol targets capture of COVID-specific parameters known to be important or potentially important at this time:

- SARS-CoV-2 qualitative testing. At Screen, subjects will typically have been identified as presumptively SARS-CoV-2 infected. The initial local SARS-CoV-2 test result will be confirmed at Screening by one of the FDA-EUA assays. The FDA-EUA assay will be used to assess SARS-CoV-2 viral presence in nasopharyngeal (preferentially) or throat swabs at periodic timepoints in this study, as indicated in Table 6-1. As this may be a relatively uncomfortable procedure for some subjects, and such sampling is biohazardous for caregivers, it is acknowledged that some subjects may not be able to provide samples for all timepoints listed. Although sampling should be encouraged at all timepoints listed through Day 14, key SARS-CoV-2 testing assessments are at Screening, Day 5 and Day 14. Sampling during follow-up is supplemental, to be collected as feasible, considering those visits are likely to be conducted via telemedicine.
- Residual eluates (in solution) from nasopharyngeal or throat swabs obtained for SARS-CoV-2 may be stored frozen for eventual quantitative testing, possible resistance analyses, and viral infectivity assays if the additional handling and storage do not impose undue exposure biohazards for site staff and the central laboratory.
- Serologic D-dimer levels, a reflector of a potential hyper-coagulopathy that is common in COVID-19 patients, for future exploratory analyses. Note: If the site uses D-dimer levels for patient management, separate D-dimer levels can be obtained locally as available, at investigator preference per their local standard of care.
- Stored serum or plasma samples will be collected for possible eventual analyses of various cytokines (including interleukin-6), antibody to SARS-CoV-2, other relevant COVID-specific tests (e.g. C-reactive protein) or SARS-CoV-2 tests (e.g. antibody tests), as reliable validated assays become available.

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Note: In an effort to standardize the method for collection of nasopharyngeal samples during the study, the same nostril in an individual subject should be used (if possible) if only one nostril will be sampled.

The sampling schedule for the above tests is specified in Table 6-1.

6.7. Pulse Oximetry

Blood oxygen saturation will be monitored by pulse oximetry, as specified in Table 6-1.

6.8. Chest Imaging

Chest imaging (chest x-ray, CT scan, etc.) will be obtained ideally at Screening but can occur within 48 hours before screening as long as the clinical status of the subject has not changed, in the opinion of the investigator. This is specified in Table 6-1. For evaluations of respiratory worsening or other AEs, additional chest imaging may be required for affected subjects during the study. Summaries of findings/radiology reports for study subjects will be captured/collected.

6.9. Assessment of Study Subject Clinical Course

Assessment of study subject signs, symptoms and daily clinical course will be conducted regularly, as specified in Table 6-1. These will include (and are not limited to):

- Daily recording of subjects' overall Clinical Status, from most severe to least severe, using a categorical scale similar to the ordinal scale of Clinical Status being used in the NIAID controlled trial design for comparatively assessing parallel study arms for treating COVID-19 patients (NCT04280705). From most severe disease to progressively less severe disease, the stages of this adapted ordinal scale of overall Clinical Status are defined as follows:
    1. Death
    2. Hospitalized, on invasive mechanical ventilation or ECMO
    3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
    4. Hospitalized, requiring supplemental oxygen
    5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
    6. Hospitalized, not requiring supplemental oxygen – no longer requires close medical care for COVID-19

       (Note: Examples include recovered subjects needing inpatient quarantining/confinement or needing social services connections for outpatient living.)
    7. Not hospitalized, but with limitation on activities and needing close outpatient care for COVID-19 manifestations
    8. Not hospitalized, no limitations on activities, no need for continued close medical care

Subjects with Status 2 or 3 disease at Screening would not be eligible for the study, but enrolled subjects who progress to respiratory failure/mechanical ventilation during the study will have deteriorated to Status 2 on this scale. It is anticipated that most "moderate" COVID-19 patients eligible for this study will be enrolled with an overall Clinical Status of 4 or 5. During the study, subjects' overall Clinical Status may worsen or improve. Maximal deteriorations will be to Status 1 (death). Deterioration to Status 2, corresponding to respiratory failure/mechanical ventilation, would require the subject to be discontinued from study treatment, and the subject would thereby be eligible for treatment with any therapies appropriate for severe COVID-19. Subjects will have achieved the secondary endpoint of "clinical recovery" with improvement to Status 6, 7 or 8.

  - Timepoints (date and time) for physicians' documented hospital discharge orders (in subjects' hospital charts) should be recorded in study subjects' electronic case record forms for this study.

- Recording (date and time) of changes in respiratory support levels for subjects' worsening or improving levels of respiratory insufficiency, according to the following ordinal scale of increasing Respiratory Support levels:
  - LEVEL 1: Normal oxygenation on room air (SpO2 ≥ 93), no need for supplemental O_2
  - LEVEL 2: Persistent hypoxemia on room air (SpO2 < 93) with requirement for low-level supplemental O_2 by nasal cannula or mask (up to 2L/min) to maintain SpO2 ≥ 93
  - LEVEL 3: Requirement for higher levels of passive supplemental O_2 by nasal cannula or mask (≥2/L min) to maintain SpO2 ≥ 93
  - LEVEL 4: Requirement for oxygenation by positive-pressure devices, e.g Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP) or other non-invasive positive-pressure respiratory support methods to maintain satisfactory oxygenation and/or ventilation
  - LEVEL 5: Requires invasive respiratory support (intubated mechanical ventilation or ECMO)
  - LEVEL 6: Death
- Level of consciousness assessment (alert-responds to voice-responds to pain-unresponsive)
- Date and time of death
- Eventual hospitalization summary details, including date of admission, reasons for hospitalization, discharge planning and date of discharge
- An assessment of signs/symptoms may also be captured at each visit.

6.10. Sparse PK Sampling

PK samples will be collected, as specified in Table 6-1, at the same time a blood sample is drawn for safety laboratory analysis. It is important that the date and time of the PK sampling is

recorded as well as the date and time of study drug administration. The sparse sampling schedule is to limit exposure of site staff to subjects with COVID-19 as well as to limit workload.

6.10.1. Sample Processing, Storage and Shipping

All PK samples will be processed, stored, and shipped according to the sample processing instructions supplied by the Sponsor or receiving laboratory.

6.10.2. Bioanalytical Methods for PK samples

Plasma concentrations of AT-527 and metabolites (as appropriate) will be measured according to validated bioanalytical methods.

Samples from all subjects who received at least one dose of AT-527 will be analyzed. Samples from subjects who received placebo will not be analyzed.

Bioanalytical laboratory personnel will have access to the randomization assignment. The bioanalytical facility will preserve the blind by reassigning alternative subject numbers for any interim data reviews.

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7. ADVERSE EVENTS

7.1. Definitions

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product(s) and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product(s), whether or not considered related to this medicinal product(s).

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug(s) caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug(s) and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug(s).

An AE may be:

- A new illness,
- Worsening of a previous chronic illness or a concomitant illness,
- An apparent adverse effect of the study medication(s) on safety-related laboratory tests. This observation could include a clinically-significant abnormal laboratory value or a significant shift from baseline (though still within normal range) which the clinical investigator or qualified designate considers to be clinically significant.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned (elective) surgical measures and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the qualified investigator).

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if they meet the definition above. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs)

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that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described above. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). Laboratory abnormalities that do not require medical intervention or action are generally not considered AEs.

Severity should be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, as described below. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.1.1. Intensity Assessment

The investigator or the designated person will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's electronic case report form (eCRF). In classification of AEs, the term "severe" is not the same as "serious". Severity is a description of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose an immediate threat to a participant's life or functioning, and meets one or more of the SAE criteria described above.

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 will be used for assessing AEs (DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017]). All AEs will be graded as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (potentially life-threatening) or grade 5 (death) according to the definitions described in the DAIDS Table. Every effort will be made to obtain an adequate evaluation of the severity.

7.1.2. Causality Assessment

The qualified investigator or a medically qualified designate will determine the relationship of any AE to study drugs using the following guidelines in Table 6-2.

Table 6-2 Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	There is evidence to suggest a causal relationship between the drug(s) and the AE (e.g., AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure).
No Reasonable Possibility	There is no evidence to suggest a causal relationship between the drug(s) and the AE.

7.2. Routine Reporting

For the purposes of this study, non-serious AEs and SAEs will be recorded in the eCRF from the time of informed consent until the end of the study.

During these periods, all AEs spontaneously reported by the subject, observed by the clinical staff, or elicited by general questioning will be recorded and reported in the eCRF.

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Any AE which remains unresolved as of the last visit will require follow-up until the AE has been resolved, a reasonable explanation for its persistence found, or is deemed chronic or stable but the investigator. It is the investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Classification will be performed by System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

In general, AEs occurring secondary to other events (e.g., clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as an SAE or AE in the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF.

7.3. Serious Adverse Event Reporting

Clinical sites must notify [redacted] of any SAE, without regard to causality, within 24 hours after becoming aware of its occurrence. Any non-serious AE which worsens and eventually meets the criteria for an SAE must also be reported as a new SAE.

Information regarding SAEs will be transmitted to [redacted] using the Serious Adverse Event form in the electronic data collection tool, which must be completed by a member of the investigational site staff within 24 hours. This form should include a clearly written narrative describing diagnostic terms, signs, symptoms and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and an assessment of the potential causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant information is available.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool and transmit to [redacted] within 24 hours by one of the following methods:

Email: [redacted]
Fax: [redacted]

The site will enter the SAE data into the electronic system as soon as it becomes available.

Contact information for the Sponsor's physician is also listed below, should the sites need to contact the Sponsor to discuss any medical, safety related questions or SAEs:

[redacted]

An unlisted (unexpected) AE is one in which the nature or severity is not consistent with the applicable product reference safety information. For investigational product(s), the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure(s). At this time in the clinical development of AT-527, based on non-clinical data and limited clinical experience to date, there are no clinical AEs or clinically significant laboratory abnormalities that

are considered to be "expected" with AT-527, at any dose level. Investigators will be notified, and the Investigator Brochure will be updated, if any pattern of AEs or laboratory abnormalities is found to be related to AT-527 dosing during studies going forward.

The start date of an SAE reported on the Serious Adverse Event form must be the same as the start date of the corresponding AE documented on the eCRF. If a change in severity is noted for the existing AE, it must be recorded. If a worsened AE meets the criteria for an SAE, the start date of the SAE must be the same as the start date of the worsened AE.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the event resolves;
- the event stabilizes;
- the event returns to baseline, if a baseline value is available;
- the event can be attributed to agents other than the study drugs or to factors unrelated to study conduct;
- it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any SAE reports will be reported by the investigators (or designee) to their local IRB/IEC in accordance with local reporting requirements and reporting timelines.

Similarly, the Sponsor (or designee) will determine whether an SAE must be reported in an expedited manner to regulatory authorities, in accordance with regulatory requirements. If so, the Sponsor (or designee) will report the event to the regulatory authorities in accord with applicable reporting timelines.

7.4. Pregnancy Reporting

All initial reports of pregnancy must be reported to [redacted] (see Section 7.3 for contact information) by the investigational staff within 24 h of their knowledge of the event using the paper Pregnancy Reporting Form provided. After the expected delivery date and/or once an outcome is known, the site will provide [redacted] with pregnancy outcome, delivery, and infant details for completion of reporting. Abnormal pregnancy outcomes are considered SAEs and must be reported using the electronic Serious Adverse Event Form. Any subject who becomes pregnant during treatment must immediately discontinue study drugs.

In addition, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 h of their knowledge of the event using the paper Pregnancy Reporting Form.

8. STATISTICAL ANALYSES

This section summarizes the statistical analyses pertinent to the efficacy and safety assessments in this study. A statistical analysis plan (SAP) describing the detailed statistical methods for this study will be prepared and finalized before database lock. Sample size calculations and power

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statements, with the exception of those for time to Clinical Recovery, were performed using SAS/STAT v9.4 (SAS Institute Inc., Cary, NC, USA). The power estimates for time to Clinical Recovery were computed by simulation. Corresponding code is provided in Section 13.

All analyses of trial data will be performed in this version of SAS/STAT or higher unless noted in the eventual SAP that other software will be utilized.

This is a double-blind randomized study, with variable size block randomization stratified by region.

In order to support interactions with regulatory agencies, the Sponsor may choose to conduct interim analyses during the course of the study. The decision to conduct an interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level.

8.1. Analysis Populations

8.1.1. Safety Population

The safety population will include all subjects who received at least one dose of the study drug (AT-527 or placebo). The study population will be analyzed as treated.

8.1.2. Intention To Treat Population

The intention to treat (ITT) population will include all randomized subjects and will be analyzed as randomized.

8.1.3. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) analysis set will contain subjects in the ITT analysis set with positive qualitative SARS-CoV-2 RT-PCR test result at baseline from the central laboratory and who receive at least one dose of study drug (AT-527 or placebo).

For analyses and displays based on mITT analysis set, subjects will be classified according to randomized treatment.

8.1.4. Per Protocol Population

The per protocol (PP) population will include the subset of the ITT subjects who completed the study drug regimen without major protocol violations that would potentially affect the study's primary endpoints.

8.1.5. PK Populations

The PK population will include all subjects who received at least one dose of AT-527 and for whom evaluable plasma concentration data are available. Subjects who received placebo will not be included in the PK population.

8.2. Endpoints

8.2.1. Primary Efficacy Endpoint and Sample Size Calculations

Part A

The primary endpoint for Part A of this study is the proportion of subjects with PRI, defined as a ≥ 2-tier increase in respiratory support methods required to maintain satisfactory oxygenation (SpO2 ≥ 93%), using the 6-tier hierarchical scale of Respiratory Support methods described in Section 6.9.

The primary efficacy goal is to reduce the incidence of PRI by 50% for active-dosed subjects compared to placebo recipients. The featured timeframe for this primary endpoint analysis will be the 14-day primary study period, with secondary analyses at study Days 10, 21, and 28.

With this study's relatively high-risk COVID-19 subject population (one or more known risk factors for poor outcomes), the study postulate is that 40% of placebo recipients will experience PRI during the 14-day study period, and the efficacy goal is therefore to reduce that incidence of PRI to 20% or less in active recipients.

Assuming PRI rates (PRIR) of 0.4 and 0.2 in the control and experimental arms, respectively, at alpha one-sided of 0.025, and at a power of 0.8, a total of 182 subjects are required at a 1:1 allocation, i.e. 91 per study arm. The study statistical hypotheses are as follows:

H_0: $Experimental_{PRIR} \geq Control_{PRIR}$

H_a: $Experimental_{PRIR} < Control_{PRIR}$

Part B

The primary endpoint of Part B is the change from baseline in amount of SARS-CoV-2 virus RNA (viral load) as measured by RT-PCR. Viral load will be assessed quantitatively using a validated assay. Analyses will be carried out at each scheduled time point using the mITT population. Part B of the study is signal seeking. The primary analysis aims to identify and characterize any potential effect of AT-527 on viral load over time. Analyses and p-values are descriptive and no adjustment for multiple comparisons will be made.

Change from baseline viral load at a timepoint will be compared between the AT-527 group and the placebo group ANCOVA with treatment as a factor and log10 baseline viral load as a covariate. In the interim analysis of the first 70 subjects from part A, the observed AT-527 effect at Day 2 was a reduction of 0.7 log10 copies/mL relative to placebo. Assuming a standard deviation for change from baseline of 1.8 log10 copies/mL and 90% of Part B randomized patients eligible for analysis (i.e. 100 patients), there is at least 90% power to detect a true treatment effect of 0.7 at a timepoint using a one-sided test at 0.1 level of significance, not adjusted for multiple comparisons.

8.2.2. Key Secondary Efficacy Endpoints

A hierarchical testing strategy to preserve study alpha when testing secondary endpoints was originally planned. The original hierarchical specifications for Part A are retained below for historical perspective. The primary endpoint for Part A is a key secondary endpoint for Part B. Following the change in protocol following the interim analysis, there will be no formal procedure to preserve study-wise type I error. All analyses are descriptive and any findings would need to be confirmed in another study with prospective alpha control.

- First Key Secondary Efficacy Endpoint: Change from baseline (CFB) in log10 SARS-CoV-2 virus RNA
- Second Key Secondary Efficacy Endpoint: Median days to Clinical Recovery (MDCR), from randomization to a disease resolution status in the NIAID Clinical Status scale described in Section 6.9 - i.e. achieving Clinical Status 6, 7, or 8 by Day 14, according to whether the subject is still hospitalized at Day 14 or is an outpatient. Patients without observed clinical recovery will have clinical recovery time assigned as 15 days to preserve the ranks for the comparison
- Third Key Secondary Efficacy Endpoint: Respiratory failure or death

  A key secondary efficacy endpoint of the study is the proportion of subjects with Respiratory Failure or Death (RFD), for which the featured assessment will be at Day 28, with additional analyses at Days 10, 14, and 63.

8.2.3. Other Secondary Efficacy Endpoints Secondary endpoints include:

- Change (improvement vs worsening) in the NIAID ordinal scale of overall Clinical Status
- All-cause mortality, to be assessed at all study timepoints, including Days 10, 14, 28, and 63
- Duration of hospitalization/confinement for COVID-19, from start of treatment to achieving Status 6, 7, or 8 on the NIAID Clinical Status scale described in Section 6.9, assessed by time-to-event analyses and by descriptive statistics
- Duration of positive SARS-CoV-2 virus detection in nasopharyngeal/throat swabs, on the schedule indicated in Table 6-1, analysed as time-to-sustained nondetectable SARS-CoV-2 RNA from randomization
- Proportion of subjects who are still SARS-CoV-2 positive at Days 5 and 14 (and longer timepoints as available)

8.2.4. Exploratory Endpoints

Exploratory endpoints include:

- Sparse plasma PK analyses, to assess PK parameters of AT-527 in COVID-19 subjects compared to PK data obtained in healthy human volunteers and HCV patients.
- Time to a National Early Warning Score (NEWS) score ≤ 2, from Screening/Baseline, for subjects whose Screening NEWS score was >4 (the NEWS score is a patient triaging score developed in Europe)

- Serial assessment of the appearance of antibody to SARS-CoV-2 in study subjects' serum samples, when validated antibody tests become more widely available
- Other relevant COVID-specific tests or SARS-CoV-2 tests that may become available

8.2.5. Safety Endpoints

Safety-related comparisons for the two treatments in this trial will include:

- Proportions of subjects experiencing SAEs
- Proportions of subjects with fatal outcomes
- Proportions of subjects experiencing AEs
  - Overall, and by body system as coded by MedDRA
- Proportions of subjects experiencing drug-attributed AEs
- Proportions of subjects experiencing graded laboratory abnormalities
  - With abnormality grades defined in the referenced DAIDS table
- Proportions of subjects discontinuing study for AEs
- Proportions of subjects discontinuing treatment for AEs

8.3. Efficacy Analysis Methods

8.3.1. Primary Efficacy Analysis

Part A

The ITT population will be the primary efficacy analysis population for Part A. Proportions of subjects (active or placebo-treated) with PRI until study completion (Day 14) will be compared by study arm. The Cochran Mantel Haenszel (CMH) test will be performed to compare the proportion of PRI rate in study arms. Stratification variables will include the randomization strata of geographic regions; additional stratification variables may be described in the eventual SAP, to be finalized prior to database lock.

Part B

Viral load will be assessed quantitatively using a validated assay. The analyses will compare change from baseline log10 viral load at each required scheduled timepoint. The analyses will be carried out on the mITT population. Change from baseline viral load will be compared between the AT-527 group and the placebo group at required post-baseline timepoint using ANCOVA with treatment as a factor and log10 baseline viral load as a covariate. The least squares mean (LSM) change and its standard error of means (SE) in each group, the differences between two groups in LSM change with corresponding 95% confidence intervals (CIs), and p-values will be presented.

8.3.2. Key Secondary Analyses

Change from baseline in amount of quantitative viral load (Part A only)

Viral load will be assessed quantitatively using a validated assay. The analyses will compare change from baseline log10 viral load at each required scheduled timepoint. Only patients with measurable viral load at baseline will be included in the analyses. Change from baseline viral load will be compared between the AT-527 group and the placebo group at each of Days 2, 5, and 14 using ANCOVA with treatment as a factor and log10 baseline viral load as a covariate. The least

squares mean (LSM) change and its standard error of means (SE) in each group, the differences between two groups in LSM change with corresponding 95% confidence intervals (CIs), and p-values will be presented. Statistical significance will be tested at Day 5, which is a time point with required sample collection in all versions of the protocol, using on one-sided 0.025 level test. If statistical significance is observed at Day 5, then Day 2 would also be tested. The Day 14 comparison will be descriptive. Descriptive summaries and comparisons at non-required timepoints may also be presented.

Median Days to Clinical Recovery

The Wilcoxon Mann-Whitney test will be utilized for the first key secondary endpoint analysis because the distribution of days until clinical recovery is not anticipated to be normally distributed.

Proportion of Subjects with Respiratory Failure or Death

This secondary endpoint will be analyzed in the same fashion as the primary endpoint, as it is similarly a proportion analysis.

8.3.3. Other Secondary Analyses

The proportions of active-treated and placebo-treated subjects improving or worsening in their Clinical Status (NIAID scale) by at least one category will be indicated in tabular displays depicting end-of-treatment data (nominal Day 5) and primary study completion data (Day 14). Analyses (active vs. placebo) will compare the probabilities of ≥1-category improvement and ≥1-category worsening - for the treatment period (Days 1-5), and the primary study period (Days 1-14).

Other secondary analyses will be delineated in the SAP and will include comparative analyses (active vs. placebo) of various efficacy and safety parameters by descriptive statistics, comparisons of proportions, and/or time-to-event analyses as appropriate.

- Assessments of all-cause mortality will include sub-analyses of deaths primarily due to respiratory failure vs. deaths attributed primarily to other causes (e.g., co-morbidities, thrombo-embolic phenomena, etc).
- Longer-term outcome data (to Days 28 and 63) will be used to evaluate subjects' longer-term COVID-19 Clinical Status, using the NIAID scale.

8.3.4. Handling of Missing Data

Patients with missing data due to death will be assigned the worst possible outcome, where applicable. Patients who do not complete D14 assessment and have study discontinuation for lack of efficacy, non-compliance with study drug, progressive disease, lost to follow-up, or adverse event will have primary endpoint response imputed as PRI. If study discontinuation reason was recovery, the primary endpoint will be imputed as no PRI. Other strategies for handling missing data will be described in the SAP.

8.4. Safety and PK Analyses

Safety Analyses

Assessing safety and tolerability of AT-527 at the selected dose will be an important objective of the study.

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Proportions of subjects experiencing SAEs, AEs, AEs resulting in treatment discontinuation and graded laboratory abnormalities will be summarized. Treatment-emergent AEs and laboratory abnormalities, defined as post-Baseline new AEs or worsened AEs, or new or worsening laboratory parameters, beginning with or after the first dose of study drug, will be included in the safety analyses. These safety-related observations will be summarized by treatment group, primarily using descriptive statistics, with use of time-to-event sub-analyses when appropriate for comparative time-related analyses of any specific clinically severe findings (e.g. death, SAEs, grade 3-4 AEs, or clinically significant grade 3-4 laboratory abnormalities).

Laboratory, ECG and vital sign data will also be summarized with descriptive statistics.

Descriptive statistics will also be used to summarize demographic variables. Other data to be summarized will include medical history, physical examination findings and concomitant medications.

PK Analyses

Plasma concentrations of study drug and metabolites in sparse samples will be listed with time data and summarized using descriptive statistics, as applicable.

Additional details regarding safety and PK analyses will be provided in the SAP.

9. ETHICS

9.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This protocol and the ICF will be submitted to an IRB or IEC prior to initiation of the study and the study will not start until the IRB or IEC, as applicable, has approved the documents.

9.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles in the latest version of the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline E6 for Good Clinical Practices (GCP) and local regulations.

9.3. Participant Information and Consent

Despite the logistical challenges of obtaining written informed consent from quarantined subjects with COVID-19, the informed consent process still must occur such that each prospective subject must be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. They will be given a copy of the ICF to review, with assistance from the study staff as needed to achieve subject understanding. Because of SARS-CoV-2 contact risks, alternative procedures for obtaining written informed consent (including signature of the ICF) may be dictated by local site policy/infection control guidelines. It is likely that the hardcopy consent form cannot leave an isolation room, and therefore may not be locally feasible as trial documentation of informed consent. If written consent by the trial participant is not feasible (because of physical isolation of the COVID-19 subject), consent can be given orally by the subject, with the consent process conducted by a study team member and confirmed by an impartial witness. In such cases, the study team member and witness would be required to sign and date the informed consent document. In addition, it could be considered that the trial participant and the persons obtaining and witnessing consent sign and date separate informed

consent forms. In either case, relevant subject consent records should be archived in the investigator site's Trial Master File.

Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained according to the locally feasible process.

9.4. Subject Confidentiality and Personal Data Protection

The investigators and the Sponsor (and contract research organization (CRO) partners) will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier on all study documents provided to the Sponsor (and CRO partners). In compliance with local regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and IRB/IEC access to review the subject's original medical records for verification of study-related procedures and data.

Supplemental Information for Participating Sites Located in the European Union (EU), as applicable

This clinical study is a process involving personal data from subjects and healthcare professionals, and as such is subject to EU general Data Protection regulation 2016/679 dated 26 April 2016, and to local laws of participating EU countries regarding personal data protection.

The investigators, the Sponsor and its contractors and sub-contractors will comply with the EU general Data Protection regulation 2016/679 date 26 April 2016 and the local laws of its participating EU countries regarding personal data protection.

The legal basis of the clinical study are legitimate interests and scientific research; the data collection and processing will be also based on the express consent of the subject that they will give in the informed consent form.

Atea Pharmaceuticals Inc. is the data controller. The clinical site(s) and other contractors and sub-contractors of Atea Pharmaceuticals Inc. are data processors.

The objective of the clinical study is research in connection with the development of therapeutics that will be commercially marketed and sold for the treatment of COVID-19.

The subjects and healthcare professionals involved in this study will be informed on the type of data collected and processed about them, for which objective and on which legal basis; they will also be informed about their rights on their personal data, and how to exercise their rights.

10. DATA COLLECTION, RETENTION, AND MONITORING

10.1. Data Safety Monitoring Board (DSMB)

A DSMB, comprising two independent clinical experts and an independent statistician, will be established to periodically assess safety and potential risk/benefit.

The DSMB will conduct planned serial safety reviews during the course of the study.

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For interim safety reviews during Part A of the study, enrollment will be paused at the following timepoints:

- After the first 20 subjects to assess safety of the 550 mg BID dosing regimen
- After the second 20 subjects

For interim safety reviews during Part B of the study, enrollment will not be paused but a safety review will be conducted at the following timepoint:

- After 50% of the Part B subjects have been enrolled.

In addition to these planned meeting, the DSMB may schedule ad hoc meetings during the course of the study.

During their reviews of data, the DSMB will have the authority to unblind data to the DSMB members, if necessary for assessing safety for an individual subject or across treatment arms. Additional details will be described in the DSMB charter. Regardless, the Sponsor, CRO, and clinical site personnel will remain treatment-blinded to all data reviewed by the DSMB, unless the DSMB promulgates a study guidance recommending study halt for efficacy, safety, or futility.

10.2. Case Report Forms

Designated site staff will use source document entries to enter the data required by the protocol into the eCRFs. Representatives of the Sponsor, the CRO or their designee(s) will train designated site staff on accessing and using a web-based Electronic Data Capture (EDC) system. Investigational site staff will not be given access to the EDC system until the required training is completed and documented. One eCRF will be completed for each subject enrolled in the study. All eCRFs will be reviewed, evaluated and approved/signed by the investigator (or designee), as required.

The original source documents and a copy of the corresponding eCRFs will be retained by the investigator. Copies of the eCRFs will be provided to the Sponsor (or designee).

10.3. Data Management and Processing

Data from eCRFs and other external data (e.g., laboratory data) will be entered into the eCRF or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

In accordance with the vendor's applicable data management procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual checks and listings. Data queries requiring clarification will be issued in the eCRF and sent to the study site for resolution. Only authorized personnel will make corrections to the clinical data in the eCRF, and all corrections will be documented in an audit trail.

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10.4. Quality Assurance

This study will be conducted in accordance with standard operating procedures (SOPs) of the CRO(s) that will conduct the study. These SOPs are designed to ensure adherence to ICH Guideline E6 for GCP.

All vendors and clinical sites will be subject to inspection by the Sponsor (or designee) to ensure that the data are generated, documented and reported in compliance with the study plan and applicable local regulatory requirements.

10.5. Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

10.6. Monitoring of the Study

Due to the COVID-19 situation, any training or monitoring described in this section may be conducted remotely or via telephone or video. Depending on the situation over time at each site, it is possible that they may be on-site.

Before study initiation, representatives of the Sponsor or its designee(s) will review the protocol and eCRF with the investigators and their staff and perform study-specific training.

During the study, the study monitor and CRO will check documentation, either remotely or on-site, to ensure completeness of records, accuracy of entries on the eCRFs, adherence to the protocol and to GCP, progress of enrollment, and confirmation study drug supply/logistics. Key study personnel must be available to assist the study monitor during remote or on-site visits.

The investigator must maintain source documents for each subject in the study, which may consist of case and visit notes (hospital or clinic medical records). All information on eCRFs must be traceable to these source documents in the subject's file. For any on-site visits, the investigator must give the study monitor access to any relevant source documents to confirm their consistency with the eCRF entries. The investigator must also keep records documenting the informed consent process. Information in source documents that could identify the subjects (such as the subjects' names) will not be forwarded to the Sponsor (or its designee(s)).

Once COVID-19 restrictions are lifted, the Sponsor or its representative(s) may visit the study facilities in order to maintain current knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will then permit any trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

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11. ADMINISTRATIVE PROCEDURES

11.1. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and local regulatory guidelines.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB/IEC for approval.

11.2. Investigator Responsibilities and Delegation of Investigator Duties

The investigator will ensure that all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator will maintain a list of sub-investigators and other appropriately qualified persons to whom he/she delegates significant trial-related duties.

11.3. Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the investigator (or designee) should promptly inform the trial subjects, should assure appropriate follow-up for the subjects and should inform the regulatory authority(ies)/IRB/IEC, when required.

11.4. Publication Policy

This is a multicenter clinical trial sponsored by Atea Pharmaceuticals. Any formal presentation or publication of data collected for this study will be considered as a joint presentation or publication by the clinical investigator(s) and the Sponsor. As is customary for multicenter trials, publication or presentation of data from individual study centers will not be allowed prior to the publication of the principal study abstract(s) and manuscript(s), without the explicit written permission of Atea Pharmaceuticals. Subsequent publications or presentations of data from the study must receive review and approval from Atea Pharmaceuticals before submission. Atea Pharmaceuticals will determine authorship of the principal study manuscript(s) in conjunction with the clinical investigator(s). All clinical investigators contributing at least one evaluable subject to the study will be considered as co-authors for the principal study manuscript(s). For such manuscript(s), masthead roles for individual clinical investigators will be determined based on subject enrollment and scientific contributions to the study.

The publication or presentation of any study results shall comply with all applicable privacy laws.

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13. APPENDIX

Appendix 1 (Applicable to Part A only)

Sample Size Code:

Primary Endpoint (SAS):

```
proc power;   twosamplefreq test=fisher
     groupproportions = (.2 .4) ntotal = .  power = .8;  run;
```

First Key Secondary Endpoint (R):

```
p nsim <- 10000
pwil <- rep(NA,nsim)
set.seed(837820122)
for (i in 1:nsim) {
  y0 <- rexp(91,log(2)/7)
  y1 <- rexp(91,log(2)/12)
  ydf <- data.frame(yt=c(y0,y1),trt=rep(0:1,c(91,91)))
  ydf$yobs <- ifelse(ydf$yt>14,15,ceiling(ydf$yt))
  pwil[i] <- wilcox.test(ydf$yobs[ydf$trt==0],ydf$yobs[ydf$trt==1],alternative="less")$p.value
}
## power
mean(pwil<0.025)
```

Second Key Secondary Endpoint (SAS):

```
proc power; twosamplefreq test=fisher groupproportions =  (0.15 0.35)
     ntotal = 182 power = .; run;
```

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Appendix 2

Update on *AT-527 Reproductive Toxicity and Non-Clinical* In Vitro Drug-Drug Interaction Data

New data from non-clinical *in vitro drug-drug interaction* and reproductive toxicity studies *have* become available since the release of the *AT-527* Investigator's Brochure Version 7. The new data are summarized below.

Overall, these new data did not provide new safety concerns and support further development. In vitro drug-drug interaction (DDI) flags *of AT-527* with potential clinical relevance were taken into account in the concomitant therapy section.

REPRODUCTIVE TOXICITY

The potential for reproductive toxicity was assessed in dose range-finding and pivotal Good Laboratory Practice (GLP)-compliant embryofetal development studies in rats and rabbits and in a GLP-compliant fertility study in the rat.

EMBRYOFETAL DEVELOPMENT

Definitive GLP-compliant embryofetal development (EFD) studies did not reveal evidence of teratogenicity or embryofetal toxicity up to the highest maternal dose level tested of 1000 mg/kg/day in rats and 100 mg/kg/day in rabbits.

Administration of AT-527 by oral gavage to female rats at dose levels of 250, 500, and 1000 mg/kg/day once daily from gestation day (GD) 7 to GD17 in an initial dose range-finding study and in a subsequent definitive study induced no maternal or developmental toxicity at any dose level.

In a dose range finding EFD study in pregnant rabbits, the two highest dose groups of 500 and 250 mg/kg/day were terminated prematurely due to severe maternal toxicity. The low dose level of 125 mg/kg/day was tolerated, but induced maternal toxicity characterized by apparent reductions of food consumption, minimal body weight loss and slightly reduced gravid uterine weight. There were no external fetal abnormalities at 125 mg/kg/day and resorption incidence was not noticeably increased, but fetal weight was reduced by 10%, which was secondary to maternal toxicity.

In a definitive GLP-compliant EFD study in pregnant rabbits, AT-527 was administered by once daily oral gavage to time-mated female New Zealand White rabbits at 25, 50, or 100 mg/kg/day from GD7 through GD19. The highest dose level of 100 mg/kg/day was above the maximum maternal tolerated dose, characterized by marked reductions in food consumption, body weight loss in the majority of rabbits and 3 associated abortions. Reductions in maternal food consumption and body weight gain were also noted at both lower dose levels of 50 and 25 mg/kg/day. Maternal administration of AT-527 did not affect embryofetal viability or fetal body weights at any dose level. There were no AT-527-related fetal abnormalities at any dose level. Therefore, the developmental no-adverse-effect level (NOAEL) for AT-527 was 100 mg/kg/day.

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FERTILITY AND EARLY EMBRYONIC DEVELOPMENT (FEED)

In a GLP-compliant FEED study, AT-527 was given to male and female rats by daily oral gavage at dose levels of 250, 500 and 1000 mg/kg/day. Males were treated for 4 weeks and females for 2 weeks before pairing. For females dosing stopped on GD6 and they were submitted to C-section on GD13. Males were dosed for at least 7 weeks prior to necropsy. Administration of AT-527 reduced body weights and body weight gains in males at 1000 mg/kg/day and caused increased incidence of abnormal breathing sounds at 500 and 1000 mg/kg/day. There were no AT-527-related effects on mating, fertility, or reproductive organ weights in males or females, estrous cycling and ovarian and uterine parameters in females, or male reproductive assessments (sperm motility or concentration) in males. Therefore, the NOAEL for AT-527 for general toxicity, reproductive performance, and early embryonic development was 1000 mg/kg/day, the highest dose tested.

Table 1 Exposures for AT-511 (Free Base Form of AT-527) and Its Major Metabolites AT-551, AT-229 and AT-273 at No-Adverse Effect Level Doses from Pivotal Reproductive Toxicity Studies

	Pivotal EFD rat 1000 mg/kg/day		Pivotal EFD rabbit 100 mg/kg/day	
	GD17 AUC_{tlast} (hr*ng/mL)	Multiple to human for 550 mg BID	GD19 AUC_{tlast} (hr*ng/mL)	Multiple to human for 550 mg BID
AT-511	145	0.02	4080	0.5
AT-551	135000	26	33800	7
AT-229	160000	10	70100	4
AT-273	28600	5	14300	2

AUC˜ area under the concentration–time curve; BID˜ twice a day; EFD˜ embryofetal development; GD˜ gestation day.

Anticipated human exposures at 550 mg BID are an AUC of 7503 hr*ng/mL for AT-511, 5134 hr*ng/mL for AT-551, 16154 hr*ng/mL for AT-229 and 6136 hr*ng/mL for AT-273.

All studies were performed in the United States with bioanalysis and toxicokinetic evaluations performed in Canada, both countries members of the Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) program. All definitive reproductive toxicity studies were performed in compliance with OECD GLP Regulations.

IN VITRO AND CLINICAL DRUG-DRUG INTERACTION

The parent compound AT--511 and metabolites AT--551, AT--229 and AT--273 were characterized in vitro to determine the potential of CYP450*, UGT1A1* and transporter-related victim and perpetrator DDI. In vitro DDI flags with potential clinical relevance were taken into account in the concomitant therapy section.

AT-511 as the parent drug is a substrate of P-glycoprotein (P-gp), and likely not a substrate of Breast Cancer Resistance protein (BCRP). The breakdown of AT511 is not CYP450 dependent, and several

catabolism/metabolism processes have been postulated and are presented in the most recent version of the Investigator's Brochure *[v7]*.

The metabolites AT-551 and AT-273 are not substrates of P-gp or BCRP, metabolite AT-229 is a substrate of BCRP but not P-gp. AT-229 is not a substrate of a renal transporter (Organic Anion Transporter 1 [OAT1] and 3 [OAT3], Organic Cation Transporter 2 [OCT2], Multidrug and Toxin Extrusion protein 1 [MATE1] and 2-K [MATE2-K]) while AT-273 is a substrate of OAT1 and OAT3 but not OCT2, MATE1, MATE2-K.

The in vitro potential of the parent drug AT-511 and the metabolites (AT-551, AT-229 and AT-273) for perpetrator DDI against drug transporters (P-gp, BCRP, Organic Anion Transporting Polypeptide 1B1 [OATP1B1] and 1B3 [OATP1B3], OAT1, OAT3, OCT2, MATE1 and MATE2-K) and CYP450's (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A) has been characterized.

AT-511 is an in vitro inhibitor of P-gp *and* BCRP with IC50 values below the estimated gut concentration (550 mg dose/intake water 250 mL) and for which a DDI risk may be anticipated. *The observed in vitro inhibition of OATP1B1 likely does not translate into a clinical relevant DDI.*

The in vitro reversible/time-dependent inhibition and induction potential of the parent drug AT-511 on CYP3A4 is likely indicated, however, the impact of the perpetrator potential on net enzyme DDI effects in liver and intestine remains uncertain. The direct inhibition IC50 values of AT-511 on CYP2C8, CYP2C19 *and UGT1A1* in vitro are much higher than the unbound systemic exposure in the historical clinical studies, and no additional CYP related in DDI risks were identified.

For metabolites AT-551, AT-229 and AT-273, no or weak perpetrator DDI risk for transporters and CYPs is anticipated based on in vitro data and the static perpetrator DDI risk assessment results.

A series of phase 1 clinical studies have been conducted/planned to assess the clinical implications of the in vitro DDI results.

Simultaneously administered CsA, a strong inhibitor of P-gp and BCRP, significantly increased plasma exposure of AT-511 but did not affect AT-229 in healthy subjects. Staggered dose of AT-527 2 hours ahead of CsA was effective in mitigating DDI risks of P-gp inhibitors.

Repeat dose of carbamazepine, a strong P-gp inducer, reduced plasma exposure of AT-511 but did not affect AT-273, plasma surrogate of the intracellular active triphosphate metabolite AT-9010. Doubling AT-527 dose to 1100 mg essentially eliminated the effect P-gp induction by carbamazepine. These results suggest that AT-527 1100 mg can be administered with strong P-gp inducers.

Repeat dose of AT-527 weakly inhibited (< 2-fold) the metabolism of midazolam, a probe substrate of CYP3A4, in healthy subjects, indicating that, among the possible effects including reversible/completive inhibition, induction and TDI, AT-511 acts overall as a weak inhibitor of CYP3A4. No dosage adjustment is therefore expected for co-medications that are CYP3A4 substrates including systemic contraceptives.