Official Title: A Multicenter, Phase III Randomized, Double-Blind, Placebo-Controlled, Outpatient Study to Evaluate the Efficacy, Safety, Antiviral Activity of RO7496998 (AT-527) in Patients With Mild or Moderate COVID-19

NCT Number: NCT04889040

Document Date: Protocol Version 3: 02-June-2021

PROTOCOL

TITLE:	**A MULTICENTER, PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, OUTPATIENT STUDY TO EVALUATE THE EFFICACY, SAFETY, AND ANTIVIRAL ACTIVITY OF RO7496998 (AT-527) IN PATIENTS WITH MILD OR MODERATE COVID-19**
PROTOCOL NUMBER:	CV43043
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-005759-18
IND NUMBER:	149508
NCT NUMBER:	To be determined
TEST PRODUCT:	RO7496998 (AT-527)
MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSORS:	F. Hoffmann-La Roche Ltd (Ex-United States) Atea Pharmaceuticals, Inc. (United States)
DATE FINAL:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date	Title	Approver's Name	Signature
June 1st 2021	[redacted] Atea Pharmaceuticals, Inc.	[redacted] M.D.	[redacted]

Date and Time (UTC)	Title	Approver's Name
02-Jun-2021 07:54:32	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
3	See electronic date stamp on title page	—	—	—
2	8 April 2021	—	—	—
1	12 February 2021	Japan	2	1 April 2021

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol CV43043 has been amended to address the feedback and questions received as part of a multinational clinical trial authorization application process. Changes to the protocol, along with a rationale for each change, are summarized below:

- Updates have been made to the Study Rationale and Benefit-Risk Assessment section to reflect recent developments in coronavirus diseases 2019 (COVID-19) treatment (Section 1.3).
- Two new secondary efficacy endpoints have been added to evaluate maintenance of symptom alleviation or improvement out to 43 hours (48 hours ±10% to allow for variability in the timing of completion of patient reported outcomes by patients) (Sections 2 and 6.4.2).
- New exploratory endpoint has been added to include optional exit interviews in order to establish supportive evidence for the COVID-19 Symptom Diary (Sections 2, 3.3.5 and 6.4.5; Appendix 1).
- The number of sites where the study will be conducted has been updated (Sections 3.1 and 9.5).
- Adolescent enrollment numbers were clarified as approximately 100 adolescent patients to match text in Sections 3.1 and 4.2 (Section 3.3.2).
- Web links to CDC adolescent growth charts were added. These were previously erroneously omitted (Section 3.3.2).
- The exclusion criterion and prohibited therapy related to prior use of amiodarone and hydroxychloroquine has been modified to exclude use within 3 months prior to screening due to the long and variable half-life of both drugs, to further mitigate any potential for drug-drug interaction with RO7496998 (AT-527) (Sections 4.1.2 and 4.4.3).
- The exclusion criterion related to prior treatment with an investigational drug has been modified to exclude use within 3 months prior to screening (Section 4.1.2).
- The exclusion criteria related to prior treatment with a COVID-19 therapeutic has been expanded and clarified to provide more examples and in response to a changing therapeutic landscape and questions from participating sites (Section 4.1.2).
- The units were standardized for the WBC, ANC, and platelet counts in the exclusion criteria (Section 4.1.2).
- It has been clarified that patients with stable chronic viral infections are eligible to participate in the study, providing other eligibility criteria are met (Section 4.1.2).
- COVID-19 vaccination within 40 days of enrollment has been added as an exclusion criteria and aligns with the information provided in the permitted therapy section. This was previously erroneously omitted from this section (Section 4.1.2).
- The permitted therapy section has been expanded and clarified in response to questions from participating sites (Section 4.4.1).

- The cautionary therapy section has been updated with additional guidance related to potential drug-drug interaction involving P-gp, BCRP and OAT1/3 drug transporters (Section 4.4.2 and Appendix 7).
- The prohibited therapy section related to treatment with a COVID-19 therapeutic has been expanded and clarified in response to a changing therapeutic landscape and questions from participating sites (Section 4.4.3).
- Footnote reference has been updated to clarify that safety samples at all visits will be analyzed locally (Appendix 1).
- The timeframe for conducting Day 33 telephone call (TC) has been modified to only allow for the TC to occur on Day 33 or the following 3 days. This will ensure adequate collection of safety data prior to study completion (Section 3.1, Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, OUTPATIENT STUDY TO EVALUATE THE EFFICACY, SAFETY, AND ANTIVIRAL ACTIVITY OF RO7496998 (AT-527) IN PATIENTS WITH MILD OR MODERATE COVID-19**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, OUTPATIENT STUDY TO EVALUATE THE EFFICACY, SAFETY, AND ANTIVIRAL ACTIVITY OF RO7496998 (AT-527) IN PATIENTS WITH MILD OR MODERATE COVID-19**
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PHASE:	Phase III
INDICATION:	COVID-19
SPONSORS:	F. Hoffmann-La Roche Ltd (Ex-United States) Atea Pharmaceuticals, Inc. (United States)

Objectives and Endpoints

This study will evaluate the efficacy, safety, antiviral activity, and pharmacokinetics of RO7496998 (AT-527) compared with placebo in non-hospitalized adults and adolescents with mild to moderate coronavirus disease 2019 (COVID-19). Specific objectives and corresponding endpoints are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of RO7496998 (AT-527) compared with placebo	• The time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 symptom diary) maintained for a duration of 21.5 hours, defined as follows: – For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary) – For preexisting symptoms: time from randomization to when a patient's symptoms have been maintained or improved (Note: Improved requires at least a single category improvement from baseline on the *COVID-19 Symptom Diary* Likert scale.)

COVID-19 = coronavirus disease 2019.

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of RO7496998 (AT-527) compared with placebo	• *The time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 Symptom Diary) maintained for a duration of 43 hours, defined as follows:* – *For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary)* – *For preexisting symptoms: time from randomization to when a patient's symptoms have been maintained or improved (Note: Improved requires at least a single category improvement from baseline on the COVID-19 Symptom Diary Likert scale.)* • Time to alleviation of *COVID-19* symptoms defined as the time from randomization to the point at which the following criterion is met and maintained for at least 21.5 hours: – Score of 0 or 1 for Items 1–12 of the COVID-19 Symptom Diary • *Time to alleviation of COVID-19 symptoms defined as the time from randomization to the point at which the following criterion is met and maintained for at least 43 hours:* – *Score of 0 or 1 for Items 1–12 of the COVID-19 Symptom Diary* • Time to one-category improvement of baseline presenting COVID-19 symptoms *(Items 1-12 of the COVID-19 Symptom Diary)* maintained for a duration of 21.5 hours defined as time from randomization to when the symptoms have improved by at least one category from baseline on the *COVID-19 Symptom Diary* Likert scale • Time to alleviation of individual symptoms, defined as the time from randomization to the point at which the following criterion is met and maintained (for each individual symptom) for at least 21.5 hours: – Score of 0 or 1 for Items 1–14 of the COVID-19 Symptom Diary • Proportion of patients requiring hospitalization for COVID-19 • Proportion of patients with ≥ 1 COVID-19 related medically attended visit through to study end (defined as hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) • Duration of fever (time to return to afebrile state [temperature ≤ 37.5°C] and remaining so for at least 21.5 hours) • Frequency of COVID-19 related complications (e.g., death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, *pericarditis/myocarditis*, cardiac failure) • Proportion of patients with any post-treatment infection • Proportion of patients with all-cause mortality

COVID-19 = coronavirus disease 2019

Secondary Objectives (cont.)	Corresponding Endpoints
• To evaluate the antiviral activity of RO7496998 (AT-527) compared with placebo	• Change from baseline in amount of SARS-CoV-2 virus RNA, as measured by RT-qPCR at each timepoint • Time to cessation of SARS-CoV-2 viral shedding, as measured by RT-qPCR • Proportion of patients positive for SARS-CoV-2 virus RNA, as measured by RT-qPCR at specified timepoints • AUC in the amount of SARS-CoV-2 virus RNA, as measured by RT-qPCR
• To evaluate the safety of RO7496998 (AT-527) compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Incidence of serious adverse events • Change from baseline in vital signs, including SpO_2 • Change from baseline in targeted clinical laboratory test results
• To characterize the PK profile of AT-511 and major metabolites in plasma	• Plasma concentration of AT-511 (the free base form of RO7496998 [AT-527]), AT-551, AT-229, and AT-273 (a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010) at specified timepoints

AUC = area under the concentration–time curve; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; RT-qPCR = reverse-transcriptase quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SpO_2 = peripheral capillary oxygen saturation.

Exploratory Objectives	Corresponding Endpoints
• To evaluate the antiviral activity of RO7496998 (AT-527) compared with placebo	• Treatment-emergent amino acid substitutions in SARS-CoV-2 viral genes (nsp12 and potentially other genes) • Anti-SARS-CoV-2 antibody status/titer at specified timepoints • Change from baseline in amount of SARS-CoV-2 virus titer at each timepoint • Time to cessation of SARS-CoV-2 viral shedding, as measured by virus titer • Proportion of patients with positive SARS-CoV-2 virus titer at specified timepoints • AUC of SARS-CoV-2 virus titer • Drug susceptibility in patients with evaluable virus at specified timepoints
• To identify and/or evaluate biomarkers that are predictive of response to RO7496998 (AT-527) (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of RO7496998 (AT-527) activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, nasopharyngeal swab, Nasosorption™, and saliva samples and efficacy, safety, PK, or other biomarker endpoints
• To evaluate health status utility, and PGIS scores of patients treated with RO7496998 (AT-527) as compared with placebo	• Patient's global impression of severity of COVID-19 symptoms as assessed through the use of PGIS at Day 14 and Day 29 • Change from baseline in EQ-5D-5L health utility index-based and VAS scores at specified timepoints
• *To support content validity of COVID-19 Symptom Diary*	• *Optional exit interviews at Day 33 (or within 14 days) in a subset of study patients to gather qualitative data to support content validity and inform interpretation of COVID-19 Symptom Diary scores observed during the study*

AUC = area under the concentration–time curve; COVID-19 = coronavirus disease 2019; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VAS = Visual Analog Scale.

Study Design

This is a Phase III, placebo-controlled, double-blind, multicenter study to assess the efficacy, safety, antiviral activity, and pharmacokinetics of RO7496998 (AT-527) compared with placebo

in non-hospitalized adult and adolescent patients with mild to moderate COVID-19 in the outpatient setting.

The study will enroll approximately 1386 patients (including approximately 100 adolescents, up to a maximum of 150, with the remaining patients being adults) with confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Patients will be randomized within 5 days of symptom onset. At the time of enrollment, patients must be stable as per eligibility criteria and not require hospitalization. Patients who, in the opinion of the treating physician are likely to experience imminent deterioration and require hospitalization will be excluded from the study. Patients confirmed to have other active viral or bacterial infections at the time of screening will be excluded.

Patients will be randomized as soon as possible after screening and within 48 hours. Patients who do not meet the criteria for participation in this study (screen failure) cannot be re-screened during the same illness episode. The investigator will record the reason for screen failure in the interactive voice or web-based response system.

Eligible patients will be randomized on or prior to Day 1 in a 2:1 ratio to receive either RO7496998 (AT-527) or matching placebo. Patients will be orally administered 550 mg RO7496998 (AT-527) or matching placebo (two 275 mg tablets) two times a day (BID) for 5 days. Randomization will be stratified by geographic region (North America, Europe and rest of the world [ROW]) and presence of a high-risk factor (yes, no). A minimum of 40% of the overall study population will have a high-risk factor for hospitalization because of COVID-19. A minimum of 40% will also be expected for the otherwise healthy population. Patients may have $\geq$1 risk factor for hospitalization as a result of COVID-19.

The study consists of two periods: a 5-day treatment period and a 28-day safety and efficacy follow-up period, with mandatory study visits on Days 1, 2, 3, 5, 7, and 14. Some of these visits may be conducted by mobile nursing or telemedicine. In addition to mandatory study visits, there will be telephone calls on Day 21 ($\pm$2 days) and Day 28 ($\pm$2 days). The end of study visit will take place on Day 33 ($+$3 days), preferentially as a telephone consult but may by conducted in-person in some instances, such as if the patient is enrolling in a longer-term follow-up RO7496998 (AT-527) study. The total study duration for each patient will be approximately 33 days.

At study visits, patients will be assessed through physical examination, vital signs including peripheral capillary oxygen saturation (SpO_2), concomitant therapies, clinical laboratory tests, nasopharyngeal (NP) swabs, Nasosorption, and saliva samples. In addition, pharmacokinetic (PK) samples will be collected from adult and adolescent patients. A cohort of 65 adult patients may also undergo optional intensive sampling for pharmacokinetics and biomarkers. Patients will be closely monitored for COVID-19 signs and symptoms, COVID-19-related medically attended visits, and adverse events; adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Throughout the treatment and safety-follow-up periods, patients will record symptoms in the COVID-19 Symptom Diary and record body temperature. Temperatures will be recorded four times daily (morning, noon, evening, and bedtime) on Days 1–5, BID (morning and evening) on Days 6–10, and once daily in the evening on Days 11–29. COVID-19 symptoms will be recorded BID (morning and bedtime) on Days 1–14 and once daily (bedtime) on Days 15–29.

If patients are hospitalized during the study treatment period, follow-up visits should continue until study end if possible.

Patients in this study may be eligible to rollover to a separate observational study for longer-term follow-up.

This study will be conducted at approximately *220* sites globally.

An external independent Data Monitoring Committee (iDMC) will evaluate safety according to policies and procedures detailed in an iDMC charter.

Number of Patients

Approximately 1386 non-hospitalized patients (including approximately 100 adolescents, up to a maximum of 150, with the remaining patients being adults) with mild to moderate COVID-19, with or without high-risk factors will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent/assent for study participation obtained from patient, parent, or patient's legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding
- Age ≥ 18 years (regardless of weight) at the time of signing informed consent or age ≥ 12 to < 18 years (weight ≥ 40 kg) at the time of signing informed consent (and assent)
- Ability to comply with all aspects of the study protocol, including providing samples for virology, in the opinion of the investigator
- At least three of the following symptoms of at least moderate (score ≥ 2 as per COVID-19 Symptom Diary) intensity: nasal congestion or runny nose, sore throat, cough, shortness of breath, muscle or body aches, fatigue, headache, chills or sweats, feeling hot or feverish, nausea, vomiting, or diarrhea.
- Positive SARS-CoV-2 diagnostic test (reverse-transcriptase polymerase chain reaction [RT-PCR] or validated rapid antigen test) ≤ 72 hours prior to randomization

  A historical record of positive result (RT-PCR and validated rapid antigen test) from test conducted ≤ 72 hours prior to randomization is acceptable. Note: sites should record the details of a patient's screening test in the eCRF. Home tests are not acceptable and would require a site confirmatory test.
- Symptoms consistent with mild or moderate COVID-19, as determined by the Investigator, with onset ≤ 5 days before randomization
- For women of childbearing potential and girls at or beyond menarche (age ≥ 12 to < 18 years): agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 30 days after the final dose of RO7496998 (AT-527).

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Women of childbearing potential must be established on their chosen method of contraception at screening.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  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.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Clinical signs indicative of COVID-19 illness requiring hospitalization defined as any of the following:
  - In adults: respiratory rate ≥ 30, heart rate ≥ 125 bpm, SpO_2 ≤ 93% on room air
  - In adolescents: respiratory rate ≥ 30, heart rate ≥ 130 bpm, SpO_2 ≤ 93% on room air
- Admitted to a hospital prior to randomization or is hospitalized (inpatient) at randomization due to COVID-19

Note: If local policy requires COVID-19 isolation or internment in a hospital or similar facility, such as in Japan, but those patients otherwise meet the inclusion criteria, this exclusion may not apply.

- In the opinion of the investigator, is likely to experience imminent deterioration and require hospitalization
- Treatment with an investigational drug within 5 half-lives or *3 months* (whichever is longer) of randomization
- Treatment with a COVID-19 therapeutic agent including, but not limited to, other direct or indirect acting antivirals *against SARS-CoV-2 (such as remdesivir or favipiravir)*, *systemic or inhaled steroids (such as dexamethasone or inhaled budesonide)*, *colchicine, ivermectin,* interferons, convalescent plasma, monoclonal antibodies against SARS CoV-2 *or interleukin 6*, intravenous immunoglobulin or other Emergency Use Authorization-approved treatments within *3 months or less than 5 drug elimination half-lives (whichever is longer)* prior to the screening visit
- Concomitant use of P-glycoprotein inhibitors or inducers listed as prohibited therapy in the protocol
- Known allergy or hypersensitivity to components of study drug
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 30 days after the final dose of RO7496998 (AT-527)

  Women of childbearing potential must have a negative pregnancy test result at screening prior to initiation of study drug.
- Abnormal laboratory test results at screening, defined as meeting any of the following sets of criteria:
  - ALT or AST $> 5 \times$ upper limit of normal (ULN)
  - Total bilirubin $> 1.5 \times$ ULN, unless the patient has known Gilbert disease
  - Creatinine clearance < 60 mL/min
  - Total WBC $< 2{,}500/\text{mm}^3$ or ANC $< 800/mm^3$
  - Platelet count $< 80/mm^3$

  Local laboratory test results from standard-of-care tests performed prior to obtaining written informed consent and ≤ 48 hours before randomization may be used; such tests do not need to be repeated for screening.
- Requirement of any prohibited medications during the study
- *Other known* active viral or bacterial infection at the time of screening*, such as influenza*

  Note: This exclusion does not apply to patients with stable chronic viral infections, such as chronic HCV or HIV providing other eligibility criteria are met.
- Any clinically significant medical condition or laboratory abnormality that, in the opinion of the investigator, could jeopardize the safety of the patient or affect patient compliance or safety/efficacy observations during the study
- *COVID-19 vaccination within ≤40-days prior to enrollment (second dose if applicable)*

End of Study

The end of this study is defined as the date when the last patient, last visit (i.e., safety follow-up telephone call), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 33 days after the last patient has been enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 months.

Investigational Medicinal Products

The investigational medicinal product for this study is RO7496998 (AT-527) or matching placebo.

Test Product (Investigational Drug)

For patients randomized to receive study drug, RO7496998 (AT-527) will be provided as 275 mg tablets; two tablets will be administered orally BID from Day 1 to Day 5.

Comparator

For patients randomized to receive placebo, placebo will be provided as 275 mg tablets; two tablets will be administered orally BID from Day 1 to Day 5.

Statistical Methods

Primary Analysis

The primary efficacy objective of this study is to evaluate the efficacy of RO7496998 (AT-527) compared with placebo in adult and adolescent patients and will be assessed based on the following endpoint:

- The time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 symptom diary) maintained for a duration of 21.5 hours (24 hours minus 10%, to allow some flexibility in the timing of assessments), defined as follows:

  For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary)

  For pre-existing symptoms: time from randomization to when a patient's symptoms have been maintained or improved (note improved requires at least a single category improvement from baseline on the *COVID-19 Symptom Diary* Likert scale)

The primary efficacy endpoint definition includes both alleviation of new COVID-19 symptoms and maintenance/improvement of pre-existing COVID-19 symptoms to allow for the possibility that some patients may have concurrent conditions with symptoms similar to those observed with COVID-19 (e.g., cough in a patient with chronic obstructive pulmonary disease). At screening, patients will be assessed with a 14-item COVID-19 symptom severity assessment to identify pre-existing symptoms (within the prior 30 days), and assess if they worsened due to COVID-19. Symptoms that are not pre-existing are considered to be new symptoms and need to achieve sustained alleviation (score of 0 or 1) to meet the endpoint.

The median time to alleviation or improvement of signs and symptoms (TTAIS) will be compared between the RO7496998 (AT-527) and placebo arms using the stratified log-rank test within three regions (i.e., North America, Europe, and ROW) and high-risk factor (yes, no) included as the stratification factors. Kaplan-Meier plots, median time to response, 95% CIs, and p-values will be presented.

The log-rank test is most powerful when the assumption of proportional hazards holds. The proportional hazards assumption will be tested graphically using the log-cumulative hazard plot by treatment group. Should the proportional hazards assumption not hold, the Gehan-Wilcoxon test will be used to analyze the data. Full details of data investigation methods and planned analysis methods will be specified in the Statistical Analysis Plan (SAP).

The estimand is the median change in time from randomization to alleviation or improvement in signs and symptoms of COVID-19 in patients with mild or moderate COVID-19. This absolute measure will be assessed during the study to Day 29 and the primary treatment effect comparison will be between the RO7496998 (AT-527) arm and the placebo arm. Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events will be accounted for through censoring rules. Patients who are lost to follow-up, who do not meet the primary endpoint, who die or discontinue for any reason prior to achieving the primary endpoint will be censored at Day 29. No dose reductions or treatment crossovers are anticipated. A treatment policy approach will be taken whereby rescue and concomitant medications will be ignored and observations collected after use will be used.

The primary efficacy analysis population will be the modified intent-to-treat infected (mITTi) population, which consists of all patients who were randomized to treatment, received a dose of

study drug, and were reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) positive for SARS-CoV-2 at any point during the study.

Determination of Sample Size

The required sample size of the mITTi population is 1248 patients. It is assumed that the RT-qPCR positive rate for SARS CoV 2 will be 90%. Therefore, approximately 1386 patients will be randomized to ensure an adequate number of patients in the mITTi population. The total number of randomized patients may change based on the percentage of patients who are RT-qPCR positive during the study.

The required sample size has been calculated to ensure at least 90% power to detect a 2 day difference in the median TTAIS of COVID 19 between the RO7496998 (AT-527) group and the placebo group, based on an assumed TTAIS in the placebo group of 10 days. Patients will be randomized to a 2:1 ratio to RO7496998 (AT-527) or placebo. The study will require 1248 patients in the mITTi population based on an expected 90% event rate (1122 events required) in order for the LogRank test to have at least 90% power with a two sided significance level of 0.025, under the assumption of an exponential distribution. Additional patients may be enrolled in order to observe 1122 events, where an event is meeting the primary endpoint.

Interim Analyses

Planned Interim Analysis

No interim analysis is planned for this study.

Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis and/or one interim virology analysis. Full details will be pre-specified in a SAP prior to the interim analysis being conducted and will include rationale and specifications for ensuring the study maintains the highest standards of integrity.

If an interim analysis is conducted for efficacy, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct the optional interim efficacy analyses, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities prior to the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If an interim analysis is conducted for virology, the Sponsor will be unblinded. The interim analysis will be conducted by the Sponsor to confirm adequate antiviral effect. Patients that contribute to the virology interim analysis will be excluded from the final efficacy and virology analyses and will be replaced in order to maintain power of the primary endpoint analysis and there will therefore be no alpha adjustment for the final analysis. The interim virology analysis will involve an early look at virology parameters over time and may include formal statistical analysis of the change from baseline in viral titer. Details will be specified in a separate interim SAP which will be finalized prior to the interim analysis taking place.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AUC	area under the concentration–time curve
BID	two times a day
BMI	body mass index
C_{max}	maximum concentration
C_{min}	minimum concentration
COVID-19	coronavirus disease 2019
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EC_{90}	90% effective concentration
eCRF	electronic Case Report Form
EDC	electronic data capture
ER	emergency room
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL	*interleukin*
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LLOQ	lower limit of quantification
MERS	middle east respiratory syndrome
mITTi	modified intention-to-treat infected
MN	mobile nursing
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NLME	non-linear mixed effects
NOAEL	no-observed-adverse effect level
NP	nasopharyngeal
NTI	narrow therapeutic index
P-gp	P-glycoprotein

Abbreviation	Definition
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PRO	patient-reported outcome
ROW	rest of the world
RT-PCR	reverse-transcriptase polymerase chain reaction
RT-qPCR	reverse-transcriptase quantitative polymerase chain reaction
SAP	Statistical Analysis Plan
SARS	severe acute respiratory syndrome
SARS-CoV-1/2	severe acute respiratory syndrome coronavirus-1/2
SpO_2	peripheral capillary oxygen saturation
T_{max}	time to maximum concentration
TTAIS	time to alleviation or improvement of signs and symptoms
ULN	upper limit of normal
VAS	Visual Analog Scale
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON COVID-19

Coronaviruses are positive-sense, single-stranded RNA viruses, named for the crown-like appearance of their spike glycoproteins on the virus envelope. They are a large family of viruses that can cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). An epidemic of cases with unexplained lower respiratory tract infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, and was reported to the WHO Country Office in China on 31 December 2019. The WHO subsequently declared a pandemic on 11 March 2020. This infectious disease, named coronavirus disease 2019 (COVID-19) by the WHO, is caused by a novel coronavirus strain SARS coronavirus-2 (SARS-CoV-2). As of 30 October 2020, nearly 45 million cases of COVID-19 and more than1 million COVID-19–related deaths were reported in over 200 countries and territories worldwide (WHO 2020).

Infection with SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illness ranging from a mild upper respiratory tract infection to severe life-threatening sepsis and multiorgan failure (Wiersinga et al. 2020). Commonly reported symptoms include fever, cough, shortness of breath, loss of taste or smell, sore throat, fatigue, headaches, muscle aches, and gastrointestinal disturbance. Symptoms are typically thought to last 2–3 weeks, but it is increasingly recognized that many patients continue to experience symptoms for many weeks, the so-called long COVID (NIHR 2020). Approximately 10% of non-hospitalized patients with mild COVID-19 report symptoms lasting more than 4 weeks, and up to 87% of hospitalized patients continue to experience symptoms 2 months after the onset of their illness. COVID-19 affects people of all ages; however, people who are immunocompromised, elderly, or have certain underlying medical conditions (e.g., chronic heart, lung, and kidney disease; diabetes, obesity, and cancer) are at increased risk of poor outcomes (Carfi et al. 2020; Centers for Disease Control [CDC] 2020a; PHE 2020).

There are now a number of vaccines with approvals or Emergency Use Authorizations (EUA) (or equivalent) for the prevention of SARS-CoV-2 infection. These remain in the early distribution phase and there are several logistical issues to be overcome in vaccinating large populations globally. Prevention and control of the disease remains a focus for public health measures to slow transmission, these include social distancing, the use of face masks, and national or regional lockdowns. Intravenous remdesivir, an inhibitor of RNA-dependent, RNA polymerase, and dexamethasone have shown benefit in hospitalized patients with COVID-19. However, in patients with moderate COVID-19, dexamethasone is not efficacious (and may be harmful), and use of remdesivir is not approved for non-hospitalized patients (Gandhi et al. 2020). There remains a significant and urgent unmet medical need for an orally administered direct acting antiviral drug with broad utility for the treatment of COVID-19. This will remain the case despite the availability of vaccinations, given that there will still be subsets of the population who will

refuse or not respond to the available vaccines, or individuals who have a contraindication and will need treatment options to be available. An antiviral therapeutic that could be administered to ambulatory, non-hospitalized patients has the potential to significantly reduce disease duration and deterioration of these patients, preventing progression of disease or hospitalization, and will have a significant impact on the pandemic and public health systems globally.

1.2 BACKGROUND ON RO7496998 (AT-527)

RO7496998 (AT-527) is a phosphoramidate prodrug of a unique 6-modified purine nucleotide prodrug discovered by Atea Pharmaceuticals Inc. In laboratory studies, RO7496998 (AT-527) potently inhibits the RNA-dependent RNA polymerase of several single-stranded RNA viruses. RO7496998 (AT-527) is converted to its active intracellular triphosphate form (AT-9010) through a series of intermediate metabolites. RO7496998 (AT-527) has demonstrated sub-micromolar potency against a range of coronaviruses, including SARS-CoV-1 (90% effective concentration [EC_{90}] = 0.34 µM) and SARS-CoV-2 (mean EC_{90} = 0.5 µM). RO7496998 (AT-527), at once daily doses up to 553 mg (free base), has been evaluated in two completed clinical studies in healthy volunteers and patients infected with hepatitis C virus (HCV). In the recently completed Phase II study (AT-01B-002), RO7496998 (AT-527) in patients infected with HCV was well-tolerated for durations of up to 12 weeks and achieved a high rate of antiviral efficacy, with no safety issues.

RO7496998 (AT-527) is administered to patients orally as tablets. In healthy volunteers and patients infected with HCV, RO7496998 (AT-527) exhibited a predictable and predictive pharmacokinetic (PK) and pharmacodynamic (PD) profile associated with the observed antiviral efficacy in patients infected with HCV. This supportive human PK profile is likely to be observed with dosing of patients with COVID-19 and is expected to be sufficient for achieving antiviral efficacy based on the sub-micromolar EC_{90} for the active triphosphate of RO7496998 (AT-527) against SARS-CoV-2 virus replication in laboratory studies.

The safety and efficacy of RO7496998 (AT-527), at doses of 550 mg twice a day (BID), in hospitalized patients age ≥18 years with moderate COVID-19 who have risk factors for poor outcome are currently being evaluated in a Phase II study (AT-03A-001).
The safety and pharmacokinetics of RO7496998 (AT-527) at doses of 550 mg BID, have also been evaluated in healthy volunteers (AT-03A-002). Summaries from these studies are briefly outlined in the sections below.

AT-03A-002

This ongoing Phase I study AT-03A-002 is a randomized (1:1), double-blind, placebo-controlled study to assess the safety and pharmacokinetics of multiple doses of RO7496998 (AT-527) in healthy subjects. *Subjects* received RO7496998 (AT-527) at doses of 550 mg or matching placebo, BID for 5 days.

Twenty subjects (10 subjects in the active group and 10 subjects in the placebo group) were enrolled and have completed dosing and follow-up through Day 10. No subjects have prematurely discontinued the study drug and no serious adverse events have been reported. All adverse events were mild, limited in duration, and were resolved by the end of the study.

There were no other clinically significant treatment-emergent laboratory abnormalities, ECG abnormalities, or vital sign abnormalities.

AT-03A-001

Phase II study AT-03A-001 is an ongoing randomized (1:1), double-blind, placebo-controlled study to evaluate the safety and efficacy of RO7496998 (AT-527) in adult patients with moderate COVID-19 who are at high risk for poor outcomes. Patients must have either obesity (BMI $>$ 30), hypertension, diabetes, or asthma. The study protocol targets enrollment of 190 patients.

Patients are treated with RO7496998 (AT-527) at doses of 550 mg or matching placebo, BID (approximately every 12 hours) for 5 days (total of 10 doses).

Safety reviews have been performed by a Data Safety Monitoring Board (DSMB) for the first two 20-patient cohorts (40 patients total) with a data cutoff date of 11 December 2020. Data remains blinded in this ongoing study. To date, pertinent events reviewed by the DSMB include:

- Serious adverse events assessed by the investigator as unrelated to study drug were reported in 3 patients: 2 patients experienced decreased oxygen saturation (1 case resulting in death due to COVID-19 pneumonia) and 1 patient experienced acute respiratory failure. Progression of COVID-19 is common in this clinical setting.
- Grade 3 or 4 adverse events of laboratory abnormalities were reported in 2 patients: in 1 patient, one event each of isolated lipase increase and isolated triglycerides increase with no associated symptoms; and in another patient, one event of hyperbilirubinemia (normal ALT/AST).
- Grade 3 and 4 laboratory abnormalities of special interest for nucleosides did not reveal any signals or patterns suggestive of drug toxicity.

Cumulative blinded data review from 40 patients enrolled in the study continues to support a favorable safety profile of RO7496998 (AT-527). The study DSMB recommended the study continue without modification.

Refer to the AT-527 Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite the availability of vaccines, a need for treatment options with varying modes of action is still required. Currently available treatments (i.e., remdesivir and

dexamethasone) have demonstrated benefit only in hospitalized patients with COVID-19. *Two virus-neutralizing monoclonal antibody cocktail therapies—bamlanivimab plus etesevimab, and casirivimab plus imdevimab—have been granted EUA for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years and older weighing at least 40 kg) 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.* These monoclonal antibody interventions are administered intravenously, and therefore, present challenges in the outpatient setting. Alternative routes of administration such as orally administered COVID-19 treatments would be more practical for use in early disease. Eventually, it is likely multiple COVID-19 therapies will be required, both to address the medical needs of distinct patient populations and to bolster treatment supplies as caseloads continue to rise worldwide. Preventing hospitalizations and chronic sequelae of COVID-19 will not only save lives but also help restore healthcare systems and other institutions that are currently overburdened by the effects of the COVID-19.

Extensive nonclinical safety data, Phase I and Phase II clinical safety data in healthy volunteers and patients infected with HCV, favorable human PK data, and the potent in vitro antiviral activity of RO7496998 (AT-527) against SARS-CoV-2 replication, support further clinical evaluation of RO7496998 (AT-527) in patients with COVID-19. The main objective of the current study is to evaluate the efficacy and safety of RO7496998 (AT-527) in patients with mild or moderate COVID-19.

Nonclinical and clinical safety studies have not revealed any pattern of drug-attributable adverse effects or any consistent clinically significant laboratory abnormalities related to any body system. Repeat dose-toxicity studies of up to 13 weeks duration in rats and monkeys did not show target organ toxicity up to the highest tested dose levels. In rats, the no-observed-adverse effect level (NOAEL) was the highest tested dose at 1000 mg/kg/day in these studies. In monkeys, the NOAEL in a 7-day study was 1000 mg/kg/day, a dose that was reduced to 650 mg/kg/day on Day 8 of a 14-day study due to loose stools, emesis, inappetence, and weight loss. The dose level of 650 mg/kg/day was the NOAEL and the highest tested dose in a subsequent 13-week monkey toxicity study. Plasma exposures achieved in these studies either exceeded or approximated the anticipated clinical exposures for the different metabolites in one or both species, depending on the metabolite. 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. These studies have not revealed a concern for reproductive toxicity and achieved exposures that exceeded the anticipated clinical exposures (see Appendix 7). Thus, the nonclinical safety data are considered to be supportive of the intended clinical dose levels and regimens and consistent with international guidelines, ICH Topic M3 (R2) and associated question and answer document (ICH 2008; ICH 2012). The

potential for gastrointestinal effects in humans will be monitored by means of medical data review and safety review on an ongoing basis in this study.

Some nucleoside analogs have been associated with mitochondrial toxicity, resulting in damage to the liver, muscles, heart, nerve, pancreas, and other organs. Nephrotoxicity has also been associated with the use of some nucleoside analogues (e.g., tenofovir), but this is not a broad class effect. The completed nonclinical assessments of RO7496998 (AT-527) indicate no potential for mitochondrial toxicity. The active triphosphate of RO7496998 (AT-527), AT-9010, 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. Additionally, using cell-based assays, RO7496998 (AT-527) had no effect on mitochondrial cell membrane integrity, mitochondrial-dependent adenosine triphosphate production or mitochondrial biogenesis. To date, there have been no clinical signs of adverse effects suggesting mitochondrial toxicity for RO7496998 (AT-527) in animal toxicology studies or in completed clinical studies.

Current medically used nucleoside analogs are primarily metabolized in the kidney, and dose adjustments are generally not needed for patients with creatinine clearance values $\geq$60 mL/min. Therefore, this study excludes patients with creatinine clearance $<$60 mL/min.

RO7496998 (AT-527) has not been associated with hepatotoxicity in nonclinical or clinical experience to date. A total of 82 subjects (30 healthy volunteers and 52 patients infected with HCV, including patients with cirrhosis), have received RO7496998 (AT-527) at various dose levels in completed clinical studies. In patients infected with HCV, liver function test values tend to normalize with RO7496998 (AT-527) treatment. No hepatotoxicity was observed in animal models (multiple species).

In the ongoing Phase I study AT-03A-002, 20 healthy subjects (10 treated with RO7496998 [AT-527] 550 mg two times a day (BID) and 10 treated with placebo) were enrolled and have completed dosing and follow-up through Day 10. No subjects have prematurely discontinued study drug. No serious adverse events have been reported and all adverse events have been mild in intensity, limited in duration, and resolved by the end of the study. There have been no other clinically significant treatment-emergent laboratory abnormalities or vital sign abnormalities. All 12-lead safety ECGs (taken Days 1, 3, and 5 prior to each dose and at 0.5 and 4 hours after each dose) were normal. In addition to these safety ECGs, continuous cardiodynamic monitoring was also performed using a Holter. This recording was performed, read, and extracted by a central ECG laboratory (ERT). Continuous Holter ECG recordings were performed from approximately 1 hour prior to the first study drug administration on Day 1 until approximately 24 hours following Day 1 a.m. dose and approximately 1 hour prior to the Day 5 a.m. dose until approximately 24 hours following Day 5 a.m. dose. ECGs were extracted at pre-determined time points, and were read centrally by ERT. Although

analysis of Holter extracted ECG data from this study is ongoing, approximately 40% of the planned ECG time points have been analyzed. To date, no significant QTcF outliers or change from baseline abnormalities have been seen. No clinically relevant changes in HR, PR, or QRS post-baseline were observed, and no clinically relevant morphologic findings were seen. Specifically, no notable conduction abnormalities, arrhythmias, ST/T wave changes, or new myocardial infarction patterns were seen. The data overall are unremarkable and consistent with expected findings within a healthy volunteer population.

In the Phase II study (AT-03A-001) evaluating RO7496998 (AT-527) 550 mg BID (compared with placebo) in hospitalized patients with moderate COVID-19 and risk factors for poor outcomes, data for the first 40 patients as of the data cutoff date of 11 December 2020 have not revealed any safety concerns.

Although it is reasonable to expect that a SARS-CoV-2 direct acting antiviral with potent in vitro antiviral activity will result in clinical benefit in patients infected with SARS-CoV-2, RO7496998 (AT-527) has not yet been proven to be efficacious in patients with COVID-19. Thus, it is possible that patients will not receive any benefit from participation in this study. However, the high unmet medical need for the treatment of COVID-19, the nonclinical and clinical data for RO7496998 (AT-527) summarized in this protocol, and the risk mitigation outlined for this study support the conduct of a placebo-controlled study to evaluate the clinical efficacy of RO7496998 (AT-527) in non-hospitalized adult and adolescent patients with mild or moderate COVID-19.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, antiviral activity, and pharmacokinetics of RO7496998 (AT-527) compared with placebo in non-hospitalized adults and adolescents with mild to moderate COVID-19. Specific objectives and corresponding endpoints (see Table 1) are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of RO7496998 (AT-527) compared with placebo	• The time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 Symptom Diary) maintained for a duration of 21.5 hours, defined as follows: – For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary) – For preexisting symptoms: time from randomization to when a patient's symptoms have been maintained or improved (Note: Improved requires at least a single category improvement from baseline on the *COVID-19 Symptom Diary* Likert scale.)
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of RO7496998 (AT-527) compared with placebo	• *The time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 Symptom Diary) maintained for a duration of 43 hours, defined as follows:* – *For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary)* – *For preexisting symptoms: time from randomization to when a patient's symptoms have been maintained or improved (Note: Improved requires at least a single category improvement from baseline on the COVID-19 Symptom Diary Likert scale.)* • Time to alleviation of *COVID-19* symptoms defined as the time from randomization to the point at which the following criterion is met and maintained for at least 21.5 hours: – Score of 0 or 1 for Items 1–12 of the COVID-19 Symptom Diary • *Time to alleviation of COVID-19 symptoms defined as the time from randomization to the point at which the following criterion is met and maintained for at least 43 hours:* – *Score of 0 or 1 for Items 1–12 of the COVID-19 Symptom Diary* • Time to one-category improvement of baseline presenting COVID-19 symptoms *(Items 1-12 of the COVID-19 Symptom Diary)* maintained for a duration of 21.5 hours defined as time from randomization to when the symptoms have improved by at least one category from baseline on the *COVID-19 Symptom Diary* Likert scale • Time to alleviation of individual symptoms, defined as the time from randomization to the point at which the following criterion is met and maintained (for each individual symptom) for at least 21.5 hours: – Score of 0 or 1 for Items 1–14 of the COVID-19 Symptom Diary • Proportion of patients requiring hospitalization for COVID-19

	• Proportion of patients with ≥ 1 COVID-19 related medically attended visit through to study end (defined as hospitalization, emergency room [ER] visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) • Duration of fever (time to return to afebrile state [temperature ≤ 37.5°C] and remaining so for at least 21.5 hours) (see Section 6.4.1) • Frequency of COVID-19 related complications (e.g., death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, *pericarditis/myocarditis*, cardiac failure) • Proportion of patients with any post-treatment infection • Proportion of patients with all-cause mortality
• To evaluate the antiviral activity of RO7496998 (AT-527) compared with placebo	• Change from baseline in amount of SARS-CoV-2 virus RNA, as measured by RT-qPCR at each timepoint • Time to cessation of SARS-CoV-2 viral shedding, as measured by RT-qPCR • Proportion of patients positive for SARS-CoV-2 virus RNA, as measured by RT-qPCR at specified timepoints • AUC in the amount of SARS-CoV-2 virus RNA, as measured by RT-qPCR
• To evaluate the safety of RO7496998 (AT-527) compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Incidence of serious adverse events • Change from baseline in vital signs, including SpO_2 • Change from baseline in targeted clinical laboratory test results
• To characterize the PK profile of AT-511 and major metabolites in plasma	• Plasma concentration of AT-511 (the free base form of RO7496998 [AT-527]), AT-551, AT-229, and AT-273 (a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010) at specified timepoints

Exploratory Objectives	Corresponding Endpoints
• To evaluate the antiviral activity of RO7496998 (AT-527) compared with placebo	• Treatment-emergent amino acid substitutions in SARS-CoV-2 viral genes (nsp12 and potentially other genes) • Anti-SARS-CoV-2 antibody status/titer at specified timepoints • Change from baseline in amount of SARS-CoV-2 virus titer at each timepoint • Time to cessation of SARS-CoV-2 viral shedding, as measured by virus titer • Proportion of patients with positive SARS-CoV-2 virus titer at specified timepoints • AUC of SARS-CoV-2 virus titer • Drug susceptibility in patients with evaluable virus at specified timepoints
• To identify and/or evaluate biomarkers that are predictive of response to RO7496998 (AT-527) (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of RO7496998 (AT-527) activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, nasopharyngeal swab, Nasosorption™, and saliva samples (listed in Section 4.5.5) and efficacy, safety, PK, or other biomarker endpoints
• To evaluate health status utility, and PGIS scores of patients treated with RO7496998 (AT-527) as compared with placebo	• Patient's global impression of severity of COVID-19 symptoms as assessed through the use of PGIS at Day 14 and Day 29 • Change from baseline in EQ-5D-5L health utility index-based and VAS scores at specified timepoints
• *To support content validity of COVID-19 Symptom Diary*	• *Optional exit interviews at Day 33 (or within 14 days) in a subset of study patients to gather qualitative data to support content validity and inform interpretation of COVID-19 Symptom Diary scores observed during the study*

AUC = area under the concentration–time curve; COVID-19 = coronavirus disease 2019; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic; PGIS = Patient Global Impression of Severity; RT-qPCR = reverse-transcriptase quantitative polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SpO_2 = peripheral capillary oxygen saturation; VAS = Visual Analog Scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, placebo-controlled, double-blind, multicenter study to assess the efficacy, safety, antiviral activity, and pharmacokinetics of RO7496998 (AT-527) compared with placebo in non-hospitalized adult and adolescent patients with mild to moderate COVID-19 in the outpatient setting.

The study will enroll approximately 1386 patients (including approximately 100 adolescents, up to a maximum of 150, with the remaining patients being adults) with confirmed SARS-COV-2 infection. Patients will be randomized within 5 days of symptom onset. At the time of enrollment, patients must be stable as per eligibility criteria and not require hospitalization. Patients who, in the opinion of the treating physician are likely to experience imminent deterioration and require hospitalization will be excluded from the study. Patients confirmed to have other active viral or bacterial infections at the time of screening will be excluded.

Patients will be randomized as soon as possible after screening and within 48 hours. Patients who do not meet the criteria for participation in this study (screen failure) cannot be re-screened during the same illness episode. The investigator will record the reason for screen failure in the interactive voice or web-based response system (IxRS).

Eligible patients will be randomized on or prior to Day 1 in a 2:1 ratio to receive either RO7496998 (AT-527) or matching placebo. Patients will be orally administered 550 mg RO7496998 (AT-527) or matching placebo (two 275 mg tablets) BID for 5 days (see Section 4.3.2.1). Randomization will be stratified by geographic region (North America, Europe and rest of the world [ROW]) and presence of a high-risk factor (yes, no). A minimum of 40% of the overall study population will have a high-risk factor for hospitalization because of COVID-19. A minimum of 40% will also be expected for the otherwise healthy population. Patients may have ≥ 1 risk factor for hospitalization as a result of COVID-19 (see Section 3.3.2).

The study consists of two periods: a 5-day treatment period and a 28-day safety and efficacy follow-up period, with mandatory study visits on Days 1, 2, 3, 5, 7, and 14. Some of these visits may be conducted by mobile nursing or telemedicine. In addition to mandatory study visits, there will be telephone calls on Day 21 (± 2 days) and Day 28 (± 2 days). The end of study visit will take place on Day 33 (+ 3 days), preferentially as a telephone consult but may by conducted in-person in some instances, such as if the

patient is enrolling in a longer-term follow-up RO7496998 (AT-527) study. The total study duration for each patient will be approximately 33 days.

Based on local COVID-19 isolation policies, such as those in Japan, some study visits may be conducted in a hospital or similar facility. Patients in these countries will meet eligibility criteria as per protocol but may be hospitalized for the sole purpose of isolation and not for severe symptoms or inpatient treatment.

At study visits, patients will be assessed through physical examination, vital signs including peripheral capillary oxygen saturation (SpO_2), concomitant therapies, clinical laboratory tests, nasopharyngeal (NP) swabs, Nasosorption, and saliva samples (see Appendix 1 for details regarding the timing of these assessments). In addition, PK samples will be collected from adult and adolescent patients at the timepoints indicated in Appendix 2. A cohort of 65 adult patients may also undergo optional intensive sampling for pharmacokinetics and biomarkers. Patients will be closely monitored for COVID-19 signs and symptoms, COVID-19-related medically attended visits, and adverse events; adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

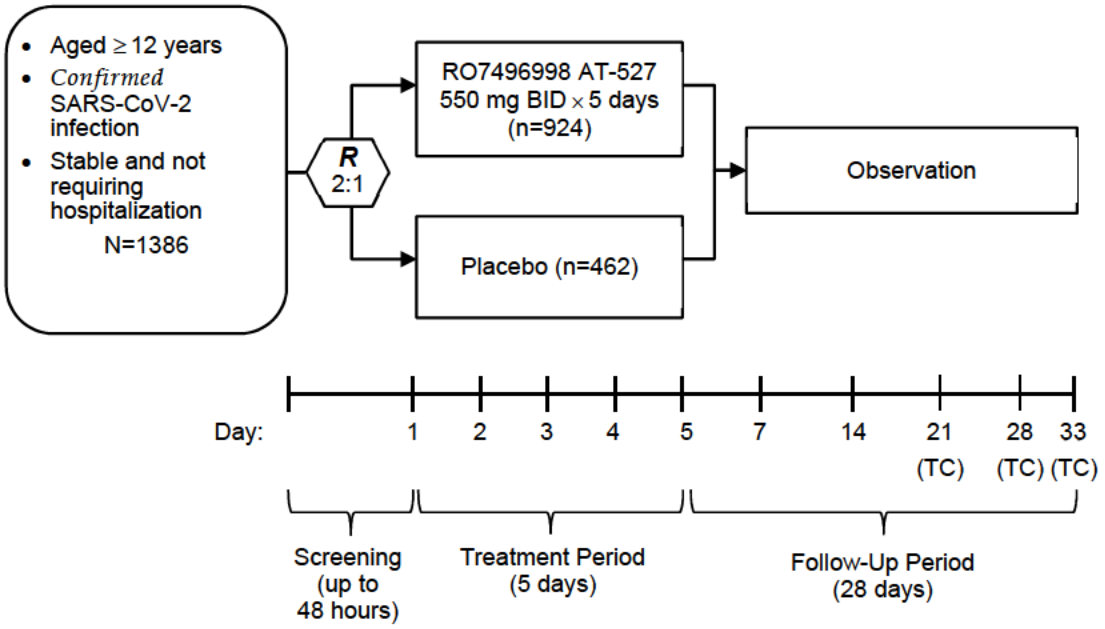
Throughout the treatment and safety-follow-up periods, patients will record symptoms in the COVID-19 Symptom Diary (see Appendix 4) and record body temperature (see Appendix 3). Temperatures will be recorded four times daily (morning, noon, evening, and bedtime) on Days 1–5, BID (morning and evening) on Days 6–10, and once daily in the evening on Days 11–29. COVID-19 symptoms will be recorded BID (morning and bedtime) on Days 1–14 and once daily (bedtime) on Days 15–29.

If patients are hospitalized during the study treatment period, follow-up visits should continue until study end if possible.

Patients in this study may be eligible to rollover to a separate observational study for longer-term follow-up.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



Randomization to 2:1 ratio (active:placebo).

BID=twice a day; R=randomization; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; TC=telephone call.

This study will be conducted at approximately *220* sites globally.

An external independent Data Monitoring Committee (iDMC) will evaluate safety according to policies and procedures detailed in an iDMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (i.e., safety follow-up telephone call), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 33 days after the last patient has been enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for RO7496998 (AT-527) Dose and Schedule

In healthy volunteers and patients infected with HCV, the pharmacokinetics of AT-511 (the free base form of RO7496998 [AT-527]), AT-551, AT-229, and AT-273 (a major nucleoside metabolite of AT-511 and a surrogate for the intracellular concentration of the active triphosphate metabolite AT-9010) were comparable. AT-511 and metabolites exhibited dose-related plasma exposure in both populations. The PK parameters of AT-511 and its metabolites AT-551, AT-229, and AT-273 were also comparable between non-cirrhotic and cirrhotic patients infected with HCV.

Similar disposition characteristics of RO7496998 (AT-527) are assumed in otherwise healthy non-hospitalized adult patients with mild or moderate COVID-19.

The RO7496998 (AT-527) dose regimen for this study is 550 mg BID for 5 days. This regimen is 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 (details in the AT-527 Investigator's Brochure).
- Predicted PK profiles for AT-9010 in the lung at the proposed 550 mg BID regimen (see the AT-527 Investigator's Brochure) show that, at steady state, the 550 mg BID regimen is predicted to deliver the following values:
  - Mean trough AT-9010 (the active triphosphate metabolite) concentrations at 12 hours 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 (see the AT-527 Investigator's Brochure)
  - Mean maximum lung AT-9010 concentrations at about 1.5 μM (time to maximum concentration [T_{max}] at about 4 hours postdose), 3-fold higher than the mean EC_{90} of 0.5 μM

While the 550 mg BID regimen has not been previously evaluated in otherwise healthy non-hospitalized adult patients with mild or moderate COVID-19, this regimen is being evaluated in the ongoing Phase II study (AT-03A-001) in hospitalized patients with moderate COVID-19 and risk factors for poor outcomes; data for the first 40 patients as of the data cutoff date of 11 December 2020 have not revealed any safety concerns. This dose has also been evaluated in healthy volunteers in the AT-03A-002 study, and has been well-tolerated, with no safety concerns.

Data for RO7496998 (AT-527) 550 mg once daily combined with daclatasvir 60 mg once daily in patients infected with HCV is available from the recently completed 12-week study (AT-01B-002). In this study, most patients received a cumulative total dose of RO7496998 (AT-527) of 30800 mg. 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 patients with COVID-19.

The animal and human systemic exposure parameters summarized in 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 RO7496998 (AT-527) 550 mg BID dose in the target population of this study.

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

In addition, a Phase II study (WV43042) to determine the antiviral activity and pharmacokinetics of RO7496998 (AT-527) at 550 mg BID for 5 days has been initiated in a similar patient population (adults only) and will provide further data to support the dosing of RO7496998 (AT-527) for this Phase III study.

3.3.2 Rationale for Patient Population

The safety and efficacy of RO7496998 (AT-527) in hospitalized adult patients with moderate COVID-19 who have risk factors for poor outcome is currently being investigated in a Phase II study (AT-03A-001). Given the significant unmet need and disease burden in those with mild to moderate disease in the outpatient setting, this Phase III study is designed to further evaluate the efficacy and safety of RO7496998 (AT-527) in this population. Using the FDA guidance for industry (FDA 2020a), mild and moderate COVID-19 baseline severity categorization is defined as follows:

- Mild COVID-19
  - Positive testing by standard reverse-transcriptase polymerase chain reaction (RT-PCR) assay or equivalent test
  - Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea
  - No clinical signs indicative of Moderate, Severe, or Critical Severity
- Moderate COVID-19
  - Positive testing by standard RT-PCR assay or equivalent testing
  - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
  - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, $SpO_2 > 93\%$ on room air at sea level, heart rate ≥ 90 beats per minute
  - No clinical signs indicative of Severe or Critical Illness Severity

In this study, *otherwise* healthy adult and adolescent patients without risk factors, as well as adult and adolescent patients with risk factors for hospitalization, will be enrolled. Randomization will be stratified based on the presence of one or more risk factors for severe COVID-19 as well as geographic region. Although the inclusion of a risk factor increases the individual risk of hospitalization, the course and progression of disease in those with mild to moderate disease alone should be similar irrespective of the presence or absence of a risk factor or the specific underlying risk factor.

The true incidence of SARS-CoV-2 infection in the pediatric population is currently unknown, and it is unclear whether adolescents are as susceptible to infection by SARS-CoV-2 compared with adults. Recent evidence suggests that those aged <18 years are likely to have the same or higher viral loads in their nasopharynx compared with adults and that adolescents can spread the virus effectively in households (Heald-Sargent et al. 2020; Park et al. 2020). Whilst children and adolescents infected with SARS-CoV-2 are less likely to develop severe illness compared with adults, they are still at risk for developing severe illness and complications from COVID-19 especially if they have underlying risk factors. Adolescents in this study will need to meet the symptom severity criteria as per adults, therefore, the benefit of RO7496998 (AT-527) is still likely to be seen in this population. *Approximately* 100 adolescents will be recruited to the study, with a maximum of 150 adolescents. Similar PK characteristics are expected for adolescents compared with adults and also in those who are healthy compared to those at high risk for poor disease outcome. It is also expected that efficacy and virological endpoints will show consistent results in adolescents compared with adults.

Although more severe COVID-19 illness can occur in individuals of all ages, it primarily occurs in older adults or those with underlying medical conditions, including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, obesity (body mass index [BMI] >30), cancer, and chronic kidney disease (CDC 2020b; Lighter et al. 2020; Wu and McGoogan 2020; Zhou et al. 2020).

The following are considered high-risk factors for hospitalization for adults and will be used for the purposes of stratification:

- Age ≥ 65 years
- Obesity, defined as BMI >30
- Cardiovascular disease, including hypertension
- Chronic lung disease, including moderate to severe asthma
- Chronic metabolic disease, including diabetes
- Chronic kidney disease
- Chronic liver disease

- Immunocompromised (e.g., active cancer, HIV or AIDS, use of corticosteroids and immunosuppressants)

The following are considered high-risk factors for hospitalization for adolescents and will be used for the purposes of stratification:

- BMI ≥ 85th percentile for their age and gender based on CDC growth chart

  Boys: https://www.cdc.gov/growthcharts/data/set1clinical/cj41l023.pdf
  Girls: https://www.cdc.gov/growthcharts/data/set1clinical/cj41l024.pdf

- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy)
- Asthma, reactive airway disease, chronic respiratory disease that requires daily medication for control
- Diabetes
- Immunosuppressive disease

3.3.3 Rationale for Control Group

A placebo-controlled study design for the evaluation of RO7496998 (AT-527) will allow unbiased evaluation of both safety and efficacy of RO7496998 (AT-527). There is a lack of targeted treatments for COVID-19 and none currently approved for those with mild-moderate disease and not requiring hospitalization. Supportive or symptomatic treatment is the mainstay of treatment for this patient population. Participants in this study will be allowed to use appropriate rescue treatment as detailed in Section 4.3.3. Therefore, a placebo-control arm is appropriate in this study.

3.3.4 Rationale for Biomarker Assessments

COVID-19 is a heterogeneous disease, and expression of certain biomarkers has been shown to vary among patients, especially those that are hospitalized (Arunachalam et al. 2020). Therefore, all patients may not be equally likely to benefit from treatment with RO7496998 (AT-527). Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with COVID-19-driven pathogenesis who are most likely to respond to RO7496998 (AT-527). PD biomarkers will also be assessed to demonstrate evidence of anti-viral activity of RO7496998 (AT-527) and the resulting changes in the host immune response in patients. Given that these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

3.3.5 Rationale for Non-Standard Clinical Outcome Assessments

At the onset of the global emergency, there was limited understanding of what constituted disease progression in COVID-19 and how the symptoms experienced by patients manifested themselves and affected their lives. Given the heterogeneous nature of COVID-19 related symptoms in outpatients, key COVID-19 related symptoms

should be assessed systematically to provide an accurate evaluation. Symptom alleviation has also been used as a registrational endpoint for influenza therapies. The precedent for the use of patient-reported symptoms in influenza provides key insights on how to apply a similar strategy to COVID-19, especially given that approximately 80% of patients with COVID-19 are treated in the outpatient setting and symptom alleviation is an important marker of clinical benefit for these patients. Furthermore, FDA guidance (FDA 2020b), notes resolution of symptoms as an example of important clinical outcomes. For this reason, the example FDA COVID-19 patient-reported outcome (PRO) instrument has been used as a basis for the COVID-19 Symptom Diary assessing 14 key symptoms and will be used for this study.
The symptom items used in this PRO are derived from information provided by the Centers for Disease Control and Prevention as of 28 August 2020. *Optional exit interviews will be conducted in a subset of patients (up to 80 patients in limited countries) to support content validity of the COVID-19 Symptom Diary.*

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1386 non-hospitalized patients (including approximately 100 adolescents, up to a maximum of 150, with the remaining patients being adults) with mild to moderate COVID-19, with or without high-risk factors will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent/assent for study participation obtained from patient, parent, or patient's legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding
- Age $\geq$18 years (regardless of weight) at the time of signing informed consent or age $\geq$12 to $<$18 years (weight $\geq$40 kg) at the time of signing informed consent (and assent)
- Ability to comply with all aspects of the study protocol, including providing samples for virology, in the opinion of the investigator
- At least three of the following symptoms of at least moderate (score $\geq$2 as per COVID-19 Symptom Diary) intensity: nasal congestion or runny nose, sore throat, cough, shortness of breath, muscle or body aches, fatigue, headache, chills or sweats, feeling hot or feverish, nausea, vomiting, or diarrhea.
- Positive SARS-CoV-2 diagnostic test (RT-PCR or validated rapid antigen test) $\leq$72 hours prior to randomization

  A historical record of positive result (RT-PCR and validated rapid antigen test) from test conducted $\leq$72 hours prior to randomization is acceptable. Note: sites should record the details of a patient's screening test in the eCRF. Home tests are not acceptable and would require a site confirmatory test.

- Symptoms consistent with mild or moderate COVID-19, as determined by the Investigator, with onset ≤5 days before randomization
- For women of childbearing potential and girls at or beyond menarche (age ≥12 to <18 years): agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 30 days after the final dose of RO7496998 (AT-527).

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Women of childbearing potential must be established on their chosen method of contraception at screening.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  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.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Clinical signs indicative of COVID-19 illness requiring hospitalization defined as any of the following:
  - In adults: respiratory rate ≥ 30, heart rate ≥ 125 bpm, SpO_2 ≤ 93% on room air
  - In adolescents: respiratory rate ≥ 30, heart rate ≥ 130 bpm, SpO_2 ≤ 93% on room air
- Admitted to a hospital prior to randomization or is hospitalized (inpatient) at randomization due to COVID-19

  Note: If local policy requires COVID-19 isolation or internment in a hospital or similar facility, such as in Japan, but those patients otherwise meet the inclusion criteria, this exclusion may not apply.

- In the opinion of the investigator, is likely to experience imminent deterioration and require hospitalization
- Treatment with an investigational drug within 5 half-lives or *3 months* (whichever is longer) of randomization
- Treatment with a COVID-19 therapeutic agent including, but not limited to, other direct or indirect acting antivirals *against SARS-CoV-2 (such as remdesivir or favipiravir)*, *systemic or inhaled steroids (such as dexamethasone or inhaled budesonide)*, *colchicine, ivermectin,* interferons, convalescent plasma, monoclonal antibodies against SARS CoV-2 *or interleukin 6 (IL-6)*, intravenous immunoglobulin or other EUA-approved treatments within *3 months or less than 5 drug elimination half-lives (whichever is longer)* prior to the screening visit
- Concomitant use of P-glycoprotein (P-gp) inhibitors or inducers listed in Section 4.4.3
- Known allergy or hypersensitivity to components of study drug
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 30 days after the final dose of RO7496998 (AT-527)

  Women of childbearing potential must have a negative pregnancy test result at screening prior to initiation of study drug.
- Abnormal laboratory test results at screening, defined as meeting any of the following sets of criteria:
  - ALT or AST $>5\times$ upper limit of normal (ULN)
  - Total bilirubin $>1.5\times$ ULN, unless the patient has known Gilbert disease
  - Creatinine clearance <60 mL/min
  - Total WBC $<2{,}500/mm^3$ or ANC $<800/mm^3$
  - Platelet count $<80/mm^3$

  Local laboratory test results from standard-of-care tests performed prior to obtaining written informed consent and ≤ 48 hours before randomization may be used; such tests do not need to be repeated for screening
- Requirement of any prohibited medications during the study
- *Other known* active viral or bacterial infection at the time of screening*, such as influenza*

  Note: This exclusion does not apply to patients with stable chronic viral infections, such as chronic HCV or HIV providing other eligibility criteria are met.
- Any clinically significant medical condition or laboratory abnormality that, in the opinion of the investigator, could jeopardize the safety of the patient or affect patient compliance or safety/efficacy observations during the study
- *COVID-19 vaccination within ≤40-days prior to enrollment (second dose if applicable); see Section 4.5.2 for documentation requirements pertaining to vaccine type and date of dosing*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS.

Patients will be randomly assigned to one of two treatment arms: RO7496998 (AT-527) or matching placebo. Randomization will occur in a 2:1 ratio of RO7496998 (AT-527) to placebo through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by region and high-risk factor for hospitalization due to COVID-19 for (see Sections 3.1 and 3.3.2 for details).

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should contact the Medical Monitor to discuss emergency unblinding after the treatment code has been broken.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to an investigational medicinal product (IMP; defined in Section 4.3). The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with

the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for this study is RO7496998 (AT-527) or matching placebo.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 RO7496998 (AT-527) and Placebo

RO7496998 (AT-527) will be supplied by the Sponsor as 275 mg tablets in high-density polyethylene bottles with child-resistant closures. For information on the formulation and handling of RO7496998 (AT-527), see the pharmacy manual.

Placebo for RO7496998 (AT-527) will be supplied by the Sponsor as matching 275 mg tablets.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation and administration.

Details regarding treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

4.3.2.1 RO7496998 (AT-527) and Placebo

RO7496998 (AT-527) is provided as 275 mg tablets; two tablets will be administered orally BID from Day 1 to Day 5. Matching placebo is provided as 275 mg tablets; two tablets will be administered orally BID from Day 1 to Day 5.

RO7496998 (AT-527) (or matching placebo) should be taken orally at 12-hour intervals (±2 hours). If the first study dose is taken prior to 2:00 p.m. on Day 1, the next dose should be taken in the evening of the same day (i.e., prior to midnight on the same calendar day with a minimum of 10 hours between doses). For these patients, the final (tenth) dose will be taken in the evening of Day 5. However, if the first study dose is taken after 2:00 p.m. on Day 1, the next dose should be taken in the morning of Day 2. For these patients, the final (tenth) dose will be taken on the morning of Day 6.

4.3.3 Rescue Medication

If COVID-19 symptoms, such as fever and headache, are so severe, in the opinion of the patient or investigator, that the patient needs rescue therapy between Day 1 and Day 29, the use of acetaminophen will be permitted only for the relief of severe symptoms. If acetaminophen is used, this should be recorded on the Concomitant Medications eCRF by the investigator, recording the dates and dosing at the next visit. Acetaminophen will not be provided by the Sponsor.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study (RO7496998 [AT-527] or matching placebo formulations) will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and AT-527 Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to RO7496998 (AT-527)

Currently, the Sponsor does not have any plans to provide Roche IMP (RO7496998 [AT-527]) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing RO7496998 (AT-527) in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED THERAPY, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days *(12 months for COVID-19 vaccines)* prior to initiation of study drug to the end of study visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

- Hormonal contraceptives (see Section 4.1.1)
- Acetaminophen *(paracetamol)*
- Hormone replacement therapy
- Prescribed medications for concomitant conditions as per medical history, *such as* antihypertensives, antidiabetic medications*, rheumatologic medications or respiratory medications (e.g., chronic inhaled/intranasal/oral steroids)*
- Low dose aspirin
- COVID-19 vaccination (see Section 4.5.2 for documentation requirements pertaining to vaccine type and date of dosing).

  Patients are not to be vaccinated during the first 2 weeks of the study.

  Patients must have *at least* a 40-day window since their last dose of vaccination (second dose if applicable) prior to enrollment.

4.4.2 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 *in vitro* experiments, AT-511 (the free base form of RO7496998) demonstrated the potential for *the following DDIs (see Appendix 7 for more details)*:

Cytochrome P450 (CYP) 3A4 sensitive substrates

- CYP3A4 induction: weak induction at mRNA level with no increase in CYP3A4 enzyme activity. The clinical relevance (e.g., potential for decreased efficacy of oral contraceptives) of this finding has not been evaluated. As a precaution, hormonal contraceptive methods in women with childbearing potential must be supplemented by a barrier method (see Section 4.1.1).
- CYP3A4 inhibition: time-dependent and reversible inhibition by AT-511. CYP3A4 sensitive substrates, in particular, those with a narrow therapeutic index (NTI), should be used with caution. Common examples of CYP3A4 sensitive substrates with NTI include aminophylline, warfarin, methotrexate and amitriptyline. A list of CYP3A4 substrates with NTI is available at: https://go.drugbank.com/categories/DBCAT004028.

  Consider substituting or stopping CYP3A4 substrates with NTI during *study* treatment and resume 2 days after the *final* dose. In the event that the CYP3A4 substrate with NTI cannot be safely discontinued or substituted, close monitoring is required.

P-glycoprotein (P-gp) sensitive substrates

- *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.

Breast Cancer Resistance Protein (BCRP) sensitive substrates

- *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.

In in vitro experiments, the plasma circulating nucleoside metabolites AT-229 and AT-273 (inactive metabolites of AT-511) demonstrated potential for the following DDI (See Appendix 7 for more details):

BCRP inhibitors or inducers

- *BCRP inhibitors or inducers may affect plasma levels of AT-229. However, AT-229 is considered an inactive metabolite, and changes in AT-229 PK are not expected to affect the antiviral activity of AT-527. Consider substituting or stopping drugs that are major BCRP inhibitors or inducers during study treatment*

and resume 12 hours after the final dose of study drug. In the event that the BCRP inhibitors or inducers cannot be safely discontinued or substituted, they should be used with caution. Common examples of BCRP inhibitors include omeprazole, lansoprazole and buprenorphine. Common examples of BCRP inducers include venlafaxine.

For a list of BCRP inhibitors and inducers, refer to https://go.drugbank.com/categories/DBCAT002662 and https://go.drugbank.com/categories/DBCAT003986, respectively.

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

- *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.

4.4.3 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:

- Investigational therapy (other than protocol-mandated study treatment)
- Treatment with a COVID-19 therapeutic agent including, but not limited to, other direct or indirect acting antivirals *against SARS-CoV-2 (such as remdesivir or favipiravir)*, *systemic or inhaled steroids (such as* dexamethasone *or inhaled budesonide)*, *colchicine, ivermectin,* interferons, convalescent plasma, monoclonal antibodies against SARS-CoV-2 *or IL-6,* intravenous immunoglobulin or other EUA-approved treatments
- Sofosbuvir, for patients with active HCV
- Abacavir for patients with HIV
- P-glycoprotein (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 in the event the P-gp inhibitor cannot be safely discontinued or substituted. If an appropriate substitute cannot be identified, dosing of *study drug* and the P-gp inhibitor must be staggered by 2 hours (with *study drug* dosed first). Patients may resume use of the substituted P-gp inhibitor approximately 12 hours after the final dose of *study drug*.

  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.

- P-gp inducers, including the following:
  - Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine
  - Rifamycins: rifabutin, rifampin, rifapentine
  - St. John's wort
  - HIV protease inhibitors (tipranavir/ritonavir)

  For other P-gp inducers, *study drug* dosing cannot be initiated unless the investigator determines that the P-gp inducer can be safely discontinued or substituted. Patients may resume use of the substituted P-gp inducers approximately 12 hours after the final dose of *study drug*.

  For a list of P-gp inducers, refer to https://go.drugbank.com/categories/DBCAT002666

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) will specify the assessments that may be performed by an MN professional.

In the event of an unscheduled visit that is not part of the schedule of activities, such as for follow-up of a medically-supervised visit or adverse event, all vital signs and activities should be documented on the unscheduled visit eCRF. As clinically indicated and where applicable, the investigator may obtain additional unscheduled assessments and labs during this visit. Examples of labs which may be appropriate include, but are not limited to, hematology, chemistry, nasopharyngeal swab, serum for biomarkers and virology, and/or blood for RNA analysis. For unscheduled visits occurring after Day 7, PK sample collection will not be recommended or required.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent/assent (where appropriate) for participation in the study must be obtained before performing any study-related procedures (including screening evaluations).

Informed Consent Forms (and Assent Forms where appropriate) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Screened patients and screen failures will be tracked in IxRS.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinical date of onset of symptoms, significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to screening will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

COVID-19 vaccination history for the 12 months before screening will be recorded in the concomitant medications eCRF, including the product or brand/trade or company manufacturer, if available (examples: Pfizer COVID-19 vaccine, Moderna COVID-19 vaccine) and date administered if known. If not available, report as COVID-19 vaccine.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. A neurologic examination, performed at screening and each subsequent study visit, should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities

should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Limited, symptom-directed physical examinations may be performed by an MN professional.

Height and weight will also be recorded at screening in all patients.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure and SpO_2 while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital sign measurement may be performed by an MN professional.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis. Collection of hematology, chemistry, coagulation and pregnancy laboratory samples will be performed locally as per schedule of activities. Historical standard-of-care laboratory tests performed locally, prior to obtaining written informed consent, may be used as the screening labs as indicated below; such tests do not need to be repeated for screening. If standard-of-care laboratory tests are conducted prior to obtaining written informed consent, documentation of results must be available.

Blood sample collection may be performed by a MN professional.

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If using a historical standard-of-care test, it must be performed ≤ 48 hours prior to randomization.
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, triglycerides, CK, CRP, ferritin, cholesterol, amylase, lipase, urate, procalcitonin, and LDH. If using a historical standard-of-care test, it must be performed ≤ 48 hours prior to randomization.
- Pregnancy test

  All women of childbearing potential will have a pregnancy test at screening. This will be a urine or serum test depending on local guidelines. If a historical serum test is conducted, it must be performed ≤ 48 hours prior to randomization.

- SARS-CoV-2 approved diagnostic test (RT-PCR or validated rapid antigen test) for screening by an NP swab. If using a historical test, it must be performed ≤ 72 hours prior to randomization.
- Coagulation: INR, aPTT, PT, D-dimer, and fibrinogen. If using a historical standard-of-care test, it must be performed ≤ 48 hours prior to randomization.

Samples for the following laboratory tests will be sent to designated central laboratories or the Sponsor or a designee for analysis:

- Plasma samples for PK analysis
- Serum samples for SARS-CoV-2 antibody titer and virology tests
- NP or nasal swabs and saliva samples for SARS-CoV-2 virology tests
- NP or nasal swabs for respiratory pathogen co-infections panel (multiplex BioFire® assay)
- Serum samples for exploratory biomarker research
- Blood PAXgene ™ RNA for RNA sequencing or quantitative PCR
- Cryopreserved peripheral blood mononuclear cells (PBMCs) for high dimensional cytometry analysis
- Plasma obtained during PBMC processing will be retained for further exploratory research
- Nasosorption samples for exploratory research on biomarkers

Consent for optional supplementary PK, PBMC and biomarker sampling (intensive sampling schedule) will be obtained at the time of study entry (see Appendix 1 and Appendix 2).

Exploratory biomarker research and virology tests may include, but will not be limited to, analysis of inflammatory mediators and/or cytokines, immune cells, virological assessment, SARS-COV-2 antibody titer, virus drug susceptibility and virus genotypic analysis (e.g., next-generation sequencing [NGS]). Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for additional PK assay development and validation, and biomarker measurements; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

- Serum, blood PAXgene RNA, PBMCs, plasma (from PBMC processing), Nasosorption, saliva, and NP swab samples collected for virology or biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board/ Ethics Committee (IRB/EC)–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.5.1 Priority Order for Blood Samples for Adolescents

Timepoints for blood samples are indicated in Appendix 1 and Appendix 2. However, in adolescents, should the total blood volume to be collected at any timepoint according to the schedule of activities exceed 0.8 mL/kg or the total blood volume per 30 day period exceed 2.4 mL/kg (adolescent patients ages 12 to <18 years and weighing 40–80 kg) the priority order for blood samples indicated in Table 2 should be followed. Note: blood volumes are based on 2008 E.U. recommendations on blood limits (EC 2020).

Table 2 Priority Order for Blood Samples for Adolescents

Order	Samples
1	Any safety laboratory samples (scheduled or unscheduled hematology, chemistry and coagulation samples and any samples performed at the discretion of the investigator)
2	Plasma PK samples
3	Serum virology/biomarker samples
4	Blood sample for RNA
5	Blood sample for WGS (optional)

PK = pharmacokinetic; WGS = whole genome sequencing.

4.5.6 Clinical Outcome Assessments

PRO instruments will be completed to assess the clinical efficacy of RO7496998 (AT-527) compared with placebo. In addition, PRO instruments will enable capture of the direct experience with RO7496998 (AT-527) for each patient.

PRO data will be collected through use of the following instruments: COVID-19 Symptom Diary, Patient Global Impression of Severity (PGIS), and EQ-5D-5L.

4.5.6.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered-at the clinic at screening and at specified timepoints during the study (see schedule of activities in Appendix 1) and at home according to prespecified timepoints. At the clinic, instruments will be administered before the patient or observer receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the instrument to be administered at each specified timepoint. The electronic device and instructions for completing the instrument electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Patients and observers should be given the following instructions for completing PRO instruments at home:

- Patients and observers should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients and observers should answer questions to the best of their ability; there are no right or wrong answers.
- Patients and observers should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During study visits and designated timepoints, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients and observers to complete the instruments
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients and observers should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.

- Patients and observers should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.6.2 Description of Clinical Outcome Assessment Instruments

COVID-19 Symptom Diary

A COVID-19 Symptom Diary (see Appendix 4) will be used to characterize key symptoms recognized as part of COVID-19 illness based on FDA guidance (FDA 2020b) and document the treatment benefit of RO7496998 (AT-527). The COVID-19 Symptom Diary is composed of 14 individual symptom item questions, each with a 3- or 4-point Likert response option.

The COVID-19 Symptom Diary will be completed in its entirety by the patient twice daily (morning and bedtime) on Days 1–14 and once daily (bedtime) on Days 15–29 (see Appendix 1). To ensure that data standards meet health authority requirements, the COVID-19 Symptom Diary will be completed as per schedule of assessment during the treatment and monitoring follow-up period.

Patient Global Impression of Severity

The PGIS (see Appendix 5) is a single item assessment of a patient's impression of the severity of his or her COVID-19 symptoms during the course of the study. Change in COVID-19 symptoms is rated on a 4-point Likert scale from "none" (0) to "severe" (3). The PGIS will be completed by the patient once a day at bedtime for the duration of the study.

EuroQol EQ-5D-5L

The EQ-5D-5L, is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 6). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.6.3 Additional COVID-19 Related Assessments

Self-Reported Temperature

Patients will measure temperature four times a day between Days 1 and 5, BID between Days 6 and 10, and once daily between Days 11 and 29 (see Appendix 3).

COVID-19 Related Medically-Attended Visit(s) Assessment

A COVID-19-related medically-attended visit will be defined as follows: hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19.

Only medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. Details will include at minimum:

- Type of visit (hospitalization, ER, urgent care, physician's office visit, telemedicine)
- Date of visit
- Primary reason for COVID-19 related medically-attended visit
- Treatments given for COVID-19 (including, but not limited to, concomitant medications and supplemental oxygen)
- If hospitalization due to COVID-19 was required, include length of visit, whether ICU care was given, or whether mechanical ventilation was required

Any adverse events or concomitant therapies reported to the investigator should be recorded on the respective Adverse Events eCRF or Concomitant Medications eCRF.

4.5.7 Optional Blood Samples for Whole Genome Sequencing (Patients at Participating Sites)

At participating sites, optional blood samples will be collected from consenting patients for DNA extraction to enable whole genome sequencing (WGS) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this section of the protocol (Section 4.5.7) will not be applicable at that site.

The Informed Consent Form will contain a separate section that addresses optional blood samples for WGS. A separate, specific signature will be required to document a patient's agreement to provide optional blood samples. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Whole Genome Sequencing Informed Consent/Withdrawal eCRF.

Genomics is increasingly informing researchers understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical

data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.5 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients who discontinue study drug prematurely will complete assessments as indicated in the schedule of activities (see Appendix 1). If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Patient Discontinuation from the Study

Patients who discontinue from study participation will return to the clinic for an early termination visit 7 (±2) days after their final dose of study drug. Patients who discontinue from the study after Day 14 will not be required to complete an early termination visit.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

RO7496998 (AT-527) is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with RO7496998 (AT-527) in completed and ongoing studies. The anticipated important safety risks for RO7496998 (AT-527) are outlined below. Please refer to the AT-527 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with RO7496998 (AT-527)

RO7496998 (AT-527), at once daily doses up to 553 mg (free base), has been evaluated in two clinical studies (AT-01B-001 and AT-01B-002) in healthy volunteers and patients infected with HCV. In the first study, 88 subjects were dosed with blinded study drug (RO7496998 [AT-527] or placebo), with 72 of the 88 subjects receiving active study drug. RO7496998 (AT-527) was well tolerated in both healthy volunteers and patients infected with HCV as either single or multiple doses (seven daily doses) up to 600 mg RO7496998 (AT-527) (equivalent to 553 mg AT-511 free base). In the second study, 10 patients infected with HCV received RO7496998 (AT-527) 550 mg in combination with 60 mg daclatasvir once daily for 8–12 weeks. There were no serious adverse events, dose-limiting toxicities, or premature discontinuations. RO7496998 (AT-527) is currently being evaluated in a Phase II study (AT-03A-001) at 550 mg BID in hospitalized patients with moderate COVID-19 and risk factors for poor outcomes. Safety data from the first 40 patients has not revealed any safety concerns (see Section 1.3). This dose has also been evaluated in healthy volunteers in the AT-03A-002 study, and has been well-tolerated, with no safety concerns (see Section 1.2).

To date, there have been no appreciable patterns of treatment-related or dose-related clinical adverse events or laboratory abnormalities from nonclinical or clinical studies.

Some nucleoside analogues have been associated with mitochondrial 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 broad class effect. The completed nonclinical assessments of RO7496998 (AT-527) indicate no potential for mitochondrial toxicity. To date, there have been no clinical signs of adverse events suggesting mitochondrial toxicity for RO7496998 (AT-527) dosing.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

There will be no dose modification for RO7496998 (AT-527) in this study.

5.1.2.2 Treatment Interruption

Treatment interruptions will not be permitted for RO7496998 (AT-527) in this study.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)

- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last study visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COVID-19.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of COVID-19, "COVID-19 progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of COVID-19

Medical occurrences or symptoms of deterioration that are anticipated as part of COVID-19, such as fluctuations in symptoms, should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening

of COVID-19 on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., accelerated worsening of COVID-19). Any COVID-19-related medically attended visits (defined as hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) should be reported in the eCRF (see Section 4.5.6.3).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization based on local COVID−19 isolation policies, such as those in Japan: patients in these countries may be hospitalized for the sole purpose of isolation and not for severe symptoms or inpatient treatment. If deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during isolation, it should be recorded as an adverse event.

5.3.5.11 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For RO7496998 (AT-527) (or matching placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with RO7496998 (AT-527) (or matching placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.12 Patient-Reported or Observer-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

PPD 24-Hour Safety Hotline:

- North America: +1 888 483 7729
- EMEA/APAC: +44 (0) 1223 374 240
- Latin America: +55 11 4504 4801

Roche Medical Monitor/ Medical Responsible: [redacted] M.D., Ph.D.

Mobile Telephone No.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 24 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 30 days after the final dose of RO7496998 (AT-527). A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior exposure to study drug. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report

these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
AT-527	AT-527 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Efficacy analyses will be conducted for the modified intent-to-treat infected (mITTi) population. This is defined as all randomized patients who received at least one dose of study drug and were centrally assessed as reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) positive for SARS-CoV-2 at any point during the study, with patients grouped according to the treatment assigned at randomization.

Safety analyses will be conducted for the safety population. This is defined as all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment received.

The analysis will occur at the end of the study (as defined in Section 3.2).

The method for controlling type I error among primary and secondary endpoints will be described in the Statistical Analysis Plan (SAP), as well as detailed specifications of the statistical methods to be implemented. The SAP will be signed off prior to unblinding.

6.1 DETERMINATION OF SAMPLE SIZE

The required sample size of the mITTi population is 1248 patients. It is assumed that the RT-qPCR positive rate for SARS-CoV-2 will be 90%. Therefore, approximately 1386 patients will be randomized to ensure an adequate number of patients in the mITTi population. The total number of randomized patients may change based on the percentage of patients who are RT-qPCR positive during the study.

Rationale for the Target Sample Size

The required sample size has been calculated to ensure at least 90% power to detect a 2-day difference in the median time to alleviation or improvement of signs and symptoms (TTAIS) of COVID-19 between the RO7496998 (AT-527) group and the placebo group, based on an assumed TTAIS in the placebo group of 10 days (Regeneron 2020). Patients will be randomized to a 2:1 ratio to RO7496998 (AT-527) or placebo, respectively, and the fixed follow-up period will be 29 days. The study will require 1248 patients in the mITTi population based on an expected 90% event rate (1122 events required) in order for the LogRank test to have at least 90% power with a two-sided significance level of 0.025, under the assumption of an exponential distribution. Additional patients may be enrolled in order to observe 1122 events, where an event is meeting the primary endpoint. The minimal detectable difference is a hazard ratio of approximately 1.15, which equates to a difference in medians of approximately 1.33 days under the assumption of a 10-day placebo response.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who are randomized, enrolled, discontinued, or completed the study will be summarized. Reasons for premature study discontinuation will be listed and summarized.

Eligibility criteria and other major protocol deviations will be listed and summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, sex, race, region, RT-PCR status, time from symptom onset to study treatment, presence of high-risk factors, pre-existing symptoms, and seropositive status at baseline) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group. These will be summarized for the mITTi population and may also be summarized for the safety population.

Medical history data, including surgery and procedures, and baseline conditions, will be summarized descriptively by treatment group using the safety population.

Previous and concomitant treatments will be summarized descriptively by treatment group, details will be specified in the SAP.

Exposure to study drug will be summarized, including number of doses. A listing of patients by treatment group, detailing dosing of study drug, will be prepared.

6.4 EFFICACY ANALYSES

Efficacy analyses will use the mITTi population, which includes all patients randomized who received at least one dose of study drug with patients grouped according to the treatment assigned at randomization and are centrally assessed RT-qPCR positive for SARS-CoV-2 at any point during the study.

In addition to the analyses described in Sections 6.4.1 and 6.4.2, the following analyses may be performed for the primary efficacy endpoint and the key secondary efficacy endpoints, as appropriate; details of these analyses will be specified in the SAP:

- Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts)
- Descriptive subgroup analyses to evaluate the consistency of results across pre-specified subgroups (e.g., based on age, sex, race/ethnicity, stratification factors, seropositive status at baseline, vaccination status, and other subgroups which may be of clinical relevance)

Hypothesis tests will be two-sided at the 2.5% significance level, unless stated otherwise.

To manage the overall type I error rate, a multiplicity strategy will be implemented, details of which will be included in the SAP prior to unblinding.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate the efficacy of RO7496998 (AT-527) compared with placebo in adult and adolescent patients and will be assessed based on the following endpoint:

- The time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 symptom diary) maintained for a duration of 21.5 hours (24 hours minus 10%, to allow some flexibility in the timing of assessments), defined as follows:
  - For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary)
  - For pre-existing symptoms: time from randomization to when a patient's symptoms have been maintained or improved (Note: Improved requires at

least a single category improvement from baseline on the *COVID-19 Symptom Diary* Likert scale)

The primary efficacy endpoint definition includes both alleviation of new COVID-19 symptoms and maintenance/improvement of pre-existing COVID-19 symptoms to allow for the possibility that some patients may have concurrent conditions with symptoms similar to those observed with COVID-19 (e.g., cough in a patient with chronic obstructive pulmonary disease). At screening, patients will be assessed with a 14-item COVID-19 symptom severity assessment to identify pre-existing symptoms (within the prior 30 days), and assess if they worsened due to COVID-19. Symptoms that are not pre-existing are considered to be new symptoms and need to achieve sustained alleviation (score of 0 or 1) to meet the endpoint.

If a symptom is pre-existing, the patient is asked if the severity at screening is worse than what was experienced within the last 30 days prior to COVID-19:

- If the severity is not worse, the symptom must be maintained (no worsening) or improved to meet the endpoint.
- If the severity is worse, then a sustained improvement of at least one grade must be achieved to meet the endpoint. For example, a symptom classed as severe at screening must improve to moderate, mild, or none, and a symptom classed as moderate at screening must improve to mild or none.

The median TTAIS will be compared between the RO7496998 (AT-527) and placebo arms using the stratified log-rank test within three regions (i.e., North America, Europe, and ROW) and high-risk factor (yes, no) included as the stratification factors. Kaplan-Meier plots, median time to response, 95% CIs, and p-values will be presented.

The log-rank test is most powerful when the assumption of proportional hazards holds. The proportional hazards assumption will be tested graphically using the log-cumulative hazard plot by treatment group. Should the proportional hazards assumption not hold, the Gehan-Wilcoxon test will be used to analyze the data. Full details of data investigation methods and planned analysis methods will be specified in the SAP.

The estimand is the median change in time from randomization to alleviation or improvement in signs and symptoms of COVID-19 in patients with mild or moderate COVID-19. This absolute measure will be assessed during the study to Day 29 and the primary treatment effect comparison will be between the RO7496998 (AT-527) arm and the placebo arm. Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events will be accounted for through censoring rules. Patients who are lost to follow-up, who do not meet the primary endpoint, who die or discontinue for any reason prior to achieving the primary endpoint will be censored at Day 29. No dose reductions or treatment crossovers are anticipated. A treatment policy approach will be taken whereby rescue

and concomitant medications will be ignored and observations collected after use will be used.

As specified in Section 6.4, the primary efficacy analysis population will be the mITTi population, which consists of all patients who were randomized to treatment, received a dose of study drug, and were RT-qPCR positive for SARS-CoV-2 at any point during the study.

Sensitivity analyses evaluating different censoring rules will be specified in the SAP. Alternative methods for evaluating TTAIS under non-proportional hazards will be specified in the SAP if required.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are as follows:

- *Time to alleviation or improvement of COVID-19 symptoms (Items 1–12 of the COVID-19 Symptom Diary) maintained for a duration of 43 hours, defined as follows:*
  - *For new symptoms: time from randomization to the alleviation of COVID-19 symptoms (i.e., a score of 0 [none] or 1 [mild] on the COVID-19 Symptom Diary)*
  - *For preexisting symptoms: time from randomization to when a patient's symptoms have been maintained or improved (Note: Improved requires at least a single category improvement from baseline on the COVID-19 Symptom Diary Likert scale.)*
- Time to alleviation of *COVID-19* symptoms defined as the time from randomization to the point at which the following criterion is met and maintained for at least 21.5 hours:
  - Score of 0 or 1 for Items 1–12 of the COVID-19 Symptom Diary
- *Time to alleviation of COVID-19 symptoms defined as the time from randomization to the point at which the following criterion is met and maintained for at least 43 hours:*
  - *Score of 0 or 1 for Items 1–12 of the COVID-19 Symptom Diary*
- Time to one-category improvement of baseline presenting COVID-19 symptoms *(Items 1-12 of the COVID-19 Symptom Diary)* maintained for a duration of 21.5 hours defined as time from randomization to when the symptoms have improved by at least one category from baseline on the *COVID-19 Symptom Diary* Likert scale
- Time to alleviation of individual symptoms, defined as the time from randomization to the point at which the following criterion is met and maintained (for each individual symptom) for at least 21.5 hours:
  - Score of 0 or 1 for Items 1–14 of the COVID-19 Symptom Diary
- Proportion of patients requiring hospitalization for COVID-19

- Proportion of patients with ≥ 1 COVID-19 related medically attended visit through to study end (defined as hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19) (see Section 4.5.6.3 for assessments to be done at weekly visits)
- Duration of fever (time to return to afebrile state [temperature ≤ 37.5°C] and remaining so for at least 21.5 hours) (see Section 6.4.1)
- Frequency of COVID-19 related complications (e.g., death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, cardiac failure)
- Proportion of patients with any post-treatment infection
- Proportion of patients with all-cause mortality

Duration and time to event secondary efficacy endpoints will be analyzed using similar methods as specified for the primary endpoint. Patients who are lost to follow-up, who do not have a response, or who die will be censored at their last contact date or date of death, whichever is applicable. Kaplan-Meier plots, median time to response, 95% CIs, and p-values will be presented.

Frequency and proportion secondary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted by the stratification factors at baseline, region (North America, Europe, ROW) and high-risk factor (yes, no), unless stated otherwise. The proportions and difference in proportions, together with a 95% CI and p-values will be presented.

COVID-19 related complications (i.e., radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, and cardiac failure) will be adjudicated per blinded manual medical review of events, together with other related eCRF data (e.g., Adverse Event forms as applicable and medical history) by an internal adjudication team before the study readout. Further details will be provided in an internal adjudication charter.

6.4.3 Secondary Virology Endpoints

The secondary virology endpoints for this study are as follows:

- Change from baseline in amount of SARS-CoV-2 virus RNA as measured by RT-qPCR at each timepoint
- Time to cessation of SARS-CoV-2 viral shedding as measured by RT-qPCR
- Proportion of patients positive for SARS-CoV-2 virus RNA by RT-qPCR at specified timepoints
- Area under the concentration curve (AUC) in the amount of SARS-CoV-2 virus RNA as measured by RT-qPCR

Continuous secondary virology endpoints, such as change from baseline endpoints, will be analyzed using an analysis of covariance (ANCOVA) model with region (North America, Europe, ROW), high-risk factor (yes, no) as stratification variables, and the baseline value of the studied measure as a covariate. The treatment group means, difference in means, along with 95% CI and p-value will be presented.

Time to event secondary virology endpoints will be analyzed using similar methods as specified for the primary endpoint. Patients who are lost to follow-up, who do not have a response, or who die will be censored at their last contact date or date of death, whichever is applicable. Kaplan-Meier plots, median time to response, 95% CIs, and p-values will be presented.

Frequency and proportion secondary virology endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted by the stratification factors at baseline, region (North America, Europe, ROW) and high-risk factor (yes, no), unless stated otherwise. The proportions and difference in proportions, together with a 95% CI and p-values will be presented.

6.4.4 Exploratory Virology Endpoints

The exploratory virology endpoints for this study are as follows:

- Treatment-emergent amino acid substitutions in SARS-CoV-2 viral genes (nsp12 and potentially other genes)
- Anti-SARS-CoV-2 antibody status/titer at specified timepoints
- Change from baseline in amount of SARS-CoV-2 virus titer at each timepoint
- Time to cessation of SARS-CoV-2 viral shedding as measured by virus titer
- Proportion of patients with positive SARS-CoV-2 virus titer at specified timepoints
- AUC of SARS-CoV-2 virus titer
- Drug susceptibility in patients with evaluable virus at specified timepoints

Time to event, incidence, proportion and change from baseline endpoints will be analyzed using the same approach as described for secondary virology endpoints.

AUC endpoints will be analyzed using the van Elteren test where AUC is calculated using the trapezoidal method. Descriptive summary statistics of the AUC will be presented for each treatment group along with the p-value from the van Elteren test for each RO7496998 (AT-527) vs placebo comparison. Additional analyses adjusting by baseline amount of virus RNA may also be conducted and will be specified in the statistical analysis plan.

Other virology endpoints will be summarized descriptively. Any further analysis methods will be specified in the SAP.

6.4.5 Exploratory Patient Reported Outcome and Health Utility Endpoints

Data from the PGIS and EQ-5D-5L will be used in separate analysis to explore psychometric properties of COVID-19 Symptom Diary and health utilities. The patient reported outcomes and health utility endpoints for this study are as follows:

- Patient's global impression of severity of COVID-19 symptoms as assessed through the use of the PGIS at Day 14 and Day 29
- Change from baseline in EQ-5D-5L health utility index-based and VAS scores at specified timepoints

  The EQ-5D-5L will be scored according to its manual, and results will be reported separately from the clinical study report.

PRO and health utility endpoints will be summarized descriptively. Any exploratory statistical analysis to be conducted on these endpoints will be documented in the SAP.

Optional Exit Interview

Data from optional exit interview responses will be used to gather and explore qualitative data. The exit interview endpoint for this study is:

- *Establishing content validity of the COVID-19 Symptom Diary and meaning of change scores observed during the study*

Exit interviews will be conducted by an external vendor. The qualitative analysis will be reported separately from the clinical study report.

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population, which will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Safety analyses will include adult and adolescent patients. Additional safety analyses divided by age subgroup may also be produced and will be specified in the SAP.

Safety will be assessed through descriptive summaries of treatment emergent adverse events (nature, frequency, severity, and causality). Adverse events will be listed. All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the NCI CTCAE v5.0 scale. Safety will be assessed through descriptive summaries of adverse events, vital sign measurements (including SpO_2), and laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts).

A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug.

Separate summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, and adverse events of special interest.

Adverse events will be summarized by MedDRA term, appropriate thesaurus level, and toxicity grade.

Descriptive summaries of laboratory values at baseline and throughout the study will be tabulated by treatment arm. For selected parameters, changes from baseline and the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

Values, along with change from baseline, will be summarized using descriptive statistics for each vital sign parameter.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g. maximum concentration [C_{max}] and minimum concentration [C_{min}]).

Samples taken for pharmacokinetic analysis will be processed and concentrations of AT-511 (free base form of AT-527) and its major metabolites will be quantified by a validated liquid chromatography-tandem mass spectrometry method. Descriptive summary statistics for PK concentration data will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. Individual and mean plasma concentration versus time data for AT-511, AT-551, AT-229, and AT-273 will be tabulated and plotted.

The following pharmacokinetic parameters will be determined on Day 1: C_{max}, T_{max} after the first dose from the plasma concentration-time data. At steady state on Day 5 the following PK parameters will be determined: $C_{max,ss}$, $T_{max,ss}$ and $C_{trough,ss}$. All PK analysis will be performed using the actual recorded sampling times for AT-511, AT-551, AT-229, and AT-273. Descriptive summary statistics for PK parameters will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is T_{max} where median, minimum, and maximum will be presented. Inter-patient variability and drug accumulation will be evaluated.

Nonlinear mixed effects (NLME) modeling will be used to analyze the dose-concentration-time data of AT-511 and AT-273 in plasma. Population and individual PK parameters (e.g., apparent clearance [CL/F] and apparent steady-state volume of distribution [Vss/F]) will be estimated and the influence of various covariates (e.g., age, gender, and body weight) on these parameters will be investigated. The data collected during this study may be pooled with data collected in other clinical studies (previous Phase I and/or Phase II study in healthy volunteers and patients infected with HCV, COVID-19) as appropriate, to build the population PK model. Secondary PK

parameters may be derived from the individual post-hoc predictions. NLME modeling results will be reported in a standalone document distinct from the clinical study report.

Additional PK analyses may be conducted as appropriate. The PK data and parameters derived from these analyses may be used for exploratory graphical analyses of the PD data and parameters.

6.7 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.8 INTERIM ANALYSIS

6.8.1 Planned Interim Analysis

No interim analysis is planned for this study.

6.8.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis and/or one interim virology analysis. Full details will be pre-specified in a SAP prior to the interim analysis being conducted and will include rationale and specifications for ensuring the study maintains the highest standards of integrity.

Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted for efficacy, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct the optional interim efficacy analyses, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities prior to the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the efficacy interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994).

Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance.

If an interim analysis is conducted for virology, the Sponsor will be unblinded. The interim analysis will be conducted by the Sponsor to confirm adequate antiviral effect. Patients that contribute to the virology interim analysis will be excluded from the final efficacy and virology analyses, and will be replaced in order to maintain power of the primary endpoint analysis and there will therefore be no alpha adjustment for the final analysis. The interim virology analysis will involve an early look at virology parameters over time and may include formal statistical analysis of the change from baseline in viral titer. Details will be specified in a separate interim SAP which will be finalized prior to the interim analysis taking place.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, electronic PRO data, and IxRS data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

An electronic device or application installed on the patient's personal device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Where permitted, study monitors will perform targeted source data verification and review to confirm that critical protocol data as defined in the Monitoring Plan and entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Due to the COVID-19 pandemic, access to clinical trial sites may be restricted. In such cases, remote source data verification (if permitted by the site and by local law) and remote data review will be performed. Study monitors will perform ongoing remote data review to confirm that critical protocol data (i.e., source data) entered on the eCRFs by authorized site personnel are accurate and complete.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

In addition to source data verification (SDV) or remote SDV on targeted critical data, ongoing remote data monitoring will be performed for this study. Study monitors will perform ongoing remote data review (defined in the Monitoring Plan and Centralized Monitoring Plan) to confirm that critical protocol data are entered into the eCRF by authorized site personnel are accurate and complete. Centralized monitoring tools will be implemented in order to support the remote data monitoring activity.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, and images, must be

retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor.
Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Centralized Monitoring Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by F. Hoffmann-La Roche Ltd (outside the United States) and Atea Pharmaceuticals, Inc. (in the United States). F. Hoffmann-La Roche Ltd will

provide clinical operations management and data management, and both, F. Hoffmann-La Roche Ltd and Atea Pharmaceuticals, Inc. will provide medical monitoring.

Approximately *220* sites globally will participate to enroll approximately 1386 patients (including approximately 100 adolescents, up to a maximum of 150, with the remaining patients being adults). Enrollment will occur through an IxRS.

A contract research organization will be used for site management and monitoring, medical monitoring, and select regulatory submissions.

An MN vendor will be used to facilitate study visits being performed within the patient's home.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, virology, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be established to monitor and evaluate patient safety throughout the study. Its composition and a description of its responsibilities will be provided in an iDMC charter.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	Screening	Treatment [a]					Monitoring						
Day	–2 to –1	1 [b]	2 [b]	3 [b]	4	5 [b]	7 [a, b]	14 [a, b]	21 (±2 days) (TC)	28 (±2 days) (TC)	33 [c, d] (+3 days) (TC)	UV	ET [b, e] (±2 days)
Informed consent	x [f]												
Demographic data	x												
Medical history and baseline conditions	x												
Symptom severity assessment	x [g]												
Pre-existing symptom assessment	x [g]												
Vital signs, including temperature and SpO_2 [h]	x	x		x		x	x	x				x	x
Height and weight	x												
Complete physical examination [i]	x												
Limited physical examination [j]		x		x		x	x	x				x	x
Medically attended visit(s) assessment [k]							x	x	x	x	x	x	x
COVID-19 Symptom Diary [l]		BID on Days 1–14							Daily on Days 15–29				x
PGIS		Daily on Days 1–29											x
EQ-5D-5L		x					x	x	x	x			x
Self-reported temperature [m]		QID on Days 1–5, BID on Days 6–10, Daily on Days 11–29											x
Hematology [n, o]	x					x						(x)	x
Chemistry [p, o]	x					x						(x)	x
Coagulation (INR, aPTT, PT, D-dimer, and fibrinogen) [o]	x					x						(x)	x
Pregnancy test [q]	x												

Appendix 1: Schedule of Activities

	Screening	Treatment [a]					Monitoring						
Day	–2 to –1	1 [b]	2 [b]	3 [b]	4	5 [b]	7 [a, b]	14 [a, b]	21 (±2 days) (TC)	28 (±2 days) (TC)	33 [c, d] (+3 days) (TC)	UV	ET [b, e] (±2 days)
Nasopharyngeal swab using a SARS-CoV-2 approved diagnostic test (RT-PCR or validated rapid antigen test)	x [r]												
Nasopharyngeal swab [s]		x [s]		x		x	x	x				(x)	x
Saliva sample [s]		x [s]	x [t]	x		x	x	x				(x)	x
Plasma PK sample		Refer to Appendix 2 for PK sampling schedule.										(x)	
Serum sample for biomarkers and virology		x				x	x	x				(x)	x
Serum sample for biomarkers (optional intensive sampling group only) [u]		x		x		x	x	x				(x)	x
Blood sample for RNA analysis		x				x	x	x				(x)	x
Blood sample for RNA analysis (optional intensive sampling group only) [u]		x		x		x	x	x				(x)	x
Blood sample for cryopreserved PBMCs (optional intensive sampling group only) [u, v]		x				x	x	x					x
Nasosorption™ sample		x [w]				x [w]		x [w]				(x)	x [w]
Blood sample for WGS (optional) [x]		x											
RO7496998 (AT-527) administration [y]		x	x	x	x	x							
Concomitant medications [z]	←	—	—	—	—	—	—	—	—	—	—	—	→
Adverse events [aa]	←	—	—	—	—	—	—	—	—	—	—	—	→

BID = two times a day; COVID-19 = coronavirus disease 2019; ET = early termination; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PGIS = Patient Global Impression of Severity; QID = four times a day; RT-PCR = reverse-transcriptase polymerase chain reaction; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus-2; SpO_2 = peripheral capillary oxygen saturation; TC = telephone call; UV = unscheduled visit; WGS = whole genome sequencing.

Notes: On treatment Day1, all assessments should be performed **prior to dosing** and on treatment Days 2–5, where possible all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 1: Schedule of Activities

Assessments in parentheses (x) should be performed as needed.

[a] For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, select assessments or procedures may be performed by a trained nursing professional at the patient's home for visits after Day 1. For patients who have provided written informed consent, procedures may be performed by a physician at the patient's home at any visit.

[b] All assessments (except sample collection) for these visits can be conducted remotely (e.g., via telephone or telemedicine), in clinic or at home.

[c] End of study visit can either be in person, telephone call or telemedicine call.

[d] *Optional exit interviews in a subset of patients to be conducted within 14 days after the Day 33 visit.*

[e] Patients who complete study treatment or discontinue study drug prematurely should continue to complete assessments as indicated until the end of the study. Patients who discontinue from study participation will return to the clinic for an early termination visit 7 (±2) days after their final dose of study drug. Patients who discontinue from the study after Day 14 will not be required to complete an early termination visit. COVID-19 Symptom Diary, PGIS, EQ-5D-5L and self-reported temperature assessments should be completed at the ET visit; one single entry will be assessed.

[f] Informed consent must be documented before any study-specific screening procedure is performed.

[g] At screening, symptom severity assessment and pre-existing symptom assessment to be done together to confirm patient eligibility.

[h] Includes SpO_2, temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position.

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary (as clinically indicated), and neurologic systems.

[j] Perform a limited, symptom-directed examination *or assessment* as clinically indicated.

[k] For patients who have provided written informed consent, the Medically Attended Visit(s) assessment can be completed by a physician/trained nursing professional at the patient's home. This assessment can also be completed via telemedicine with a physician or at site. All details to be recorded in the eCRF at all visits. For details of the assessment see Section 4.5.6.3.

[l] The COVID-19 Symptom Diary will be completed by the patient twice daily on Days 1–14, this questionnaire should be completed in the morning and bedtime. On Day 1, the first diary questionnaire should be completed prior to the first dose. Then on Days 15–29, the COVID-19 Symptom Diary will be completed once daily at bedtime.

[m] Body temperature should be assessed and recorded by the patient four times daily (morning, noon, evening, and bedtime) on Days 1–5, BID (morning and evening) on Days 6–10, and once daily (evening) on Days 11–29.

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[o] *Safety* samples (hematology, chemistry and coagulation) will be analyzed locally. Refer to Section 4.5.5 for information regarding the acceptability of historical standard-of-care tests.

[p] Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, triglycerides, CK, CRP, ferritin, cholesterol, amylase, lipase, urate, procalcitonin, and LDH.

[q] All women of childbearing potential will have a pregnancy test at screening. This will be performed locally and will be a urine or serum test, depending on local guidelines. Refer to Section 4.5.5 for information regarding the acceptability of historical standard-of-care tests.

[r] Performed at or prior to Screening, nasopharyngeal swabs will be analyzed for the SARS-CoV-2 by approved diagnostic test (RT-PCR or validated rapid antigen test) locally.

[s] Swab samples and saliva samples should be collected at approximately the same time every day where possible. The sample on Day 1 should be collected **prior to dosing**. At least two nasopharyngeal swabs, one from each nostril, will be taken at each visit. Should the patient decline a nasopharyngeal swab, a nasal swab from each nostril may be collected instead.

[t] For saliva sample at Day 2 only: patients can take the sample at home and bring to site on Day 3 (if they are having on-site visits) or the mobile nurse/physician can pick the sample up at Day 3 (if they have consented to home visits).

[u] Optional samples collected in adult patients only and who have consented to PK and biomarker intensive sampling.

[v] A plasma sample will be generated from the blood sample obtained following PBMC processing and will be stored for biomarker research. No additional blood draw is needed. Samples for PBMC may not be collected at some timepoints if sample stability requirements for processing will not be met. Please refer to the laboratory manual for more details.

[w] At Day 1, Day 5, Day 14 and ET, Nasosorption sample to be taken after the nasopharyngeal swabs.

[x] Not applicable for a site that has not been granted approval for WGS. Performed only for patients at participating sites who have provided written informed consent to participate. If the sample is not collected at the Day 1 visit for any reason, it may be collected at any later timepoint.

[y] Study treatment will be administered BID to be taken 12 hours apart for a total of 10 doses. See Section 4.3.2.1 for details.

[z] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and supplemental oxygen used by a patient in addition to protocol-mandated treatment from 7 days *(12 months for COVID-19 vaccines)* prior to initiation of study drug until the end of study follow-up on Day 33, will be recorded. Any COVID-19 vaccination which has occurred before the patient enrolls into the study or during the study will be recorded in the concomitant medications eCRF, including the product or brand/trade or company manufacturer, if available (examples: Pfizer COVID-19 vaccine, Moderna COVID-19 vaccine) and date administered if known. If not available, report as COVID-19 vaccine.

[aa] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until the end of study follow-up telephone call on Day 33.

Appendix 2
Schedule of Pharmacokinetic Samples (for Adults and Adolescents)

Visit	Timepoint	Sample Type
PK sparse sampling [a]		
Day 1 (with reference to 1st dose)	Predose (–30 min)	RO7496998 (AT-527) PK (plasma)
	1 hour postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
Day 5 (with reference to the morning dose)	Predose (–30 min)	RO7496998 (AT-527) PK (plasma)
	1 hour postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
Day 7	Anytime [c]	RO7496998 (AT-527) PK (plasma)
Optional PK intensive sampling [b]		
Day 1 (with reference to the 1st dose)	Predose (–30 min)	RO7496998 (AT-527) PK (plasma)
	1 hour postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
	2 hours postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
	4 hours postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
Day 5 (with reference to the morning dose)	Predose (–30 min)	RO7496998 (AT-527) PK (plasma)
	1 hour postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
	2 hours postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
	4 hours postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
	8 hours postdose (±30 min)	RO7496998 (AT-527) PK (plasma)
Day 7	Anytime [c]	RO7496998 (AT-527) PK (plasma)

PK = pharmacokinetic.

[a] PK samples to be collected in adult and adolescent patients. Samples can be collected and processed in clinic/at site or at home (if patients consented to home visits).

[b] Optional PK samples to be collected in adult patients only, and who have consented to PK intensive sampling. Samples to be collected and processed at site only.

[c] The exact sampling time will be captured in relation to the time of last (10th) dose.

Appendix 3
Temperature

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Temperature:

Please take your temperature now.

What is your temperature right now? (Measure before taking fever medication): _____ (Choose °C or °F)

Appendix 4
COVID-19 Symptom Diary

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Note that the following is a sample. Sites will be provided with separate versions of the diary, reflecting appropriate recall periods.

COVID-19 Symptom Diary (Morning)

This diary will keep track of your COVID-19 symptoms and temperature during the study. Please complete this diary when you first wake up in the morning (before getting out of bed). Remember to take your temperature before you take any medicines to help your COVID-19 symptoms.

Please rate the severity of each symptom at its worst since you went to bed last night.

	None 0	Mild 1	Moderate 2	Severe 3
1. Nasal Congestion or runny nose				
2. Sore Throat				
3. Cough				
4. Shortness of breath (difficulty breathing)				
5. Muscle or body aches				
6. Fatigue (tiredness)				
7. Headache				
8. Chills/Sweats				
9. Feeling hot or feverish				
10. Nausea (wanting to throw up)				
11. Vomiting (thrown up)				
12. Diarrhea (mostly or completely liquid bowel movements)				

	Same as usual 0	**Less than usual 1**	**No sense 2**
13. Rate your sense of **smell** since you went to bed last night.			
14. Rate your sense of **taste** since you went to bed last night.			

Appendix 5
Patient Global Impression of Severity

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Patient Global Impression of Severity (Bedtime)

Please rate your overall COVID-19 symptoms at their worst in the past 24 hours.

☐ None

☐ Mild

☐ Moderate

☐ Severe

Appendix 6
EuroQol 5-Dimension, 5-Level Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

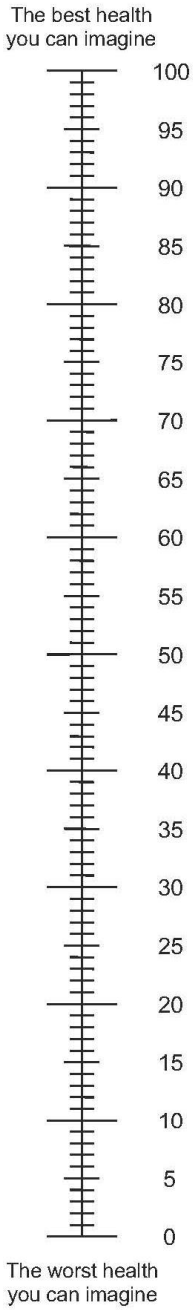
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7
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 including the planned Phase 3 clinical trial. 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.

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 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 AT-511 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.