

# CLINICAL STUDY PROTOCOL

## A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO -CONTROLLED, DOSE-RANGING TRIAL TO EVALUATE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF AT-752 IN PATIENTS WITH DENGUE INFECTION

### PROTOCOL NO. AT-02A-002

**Sponsor:** Atea Pharmaceuticals, Inc.  
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### CONFIDENTIAL

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Atea Pharmaceuticals, Inc.

The study will be conducted according to this Protocol, the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice and applicable Regulatory Requirements.

#### CONFIDENTIALITY STATEMENT

The information provided in this document is strictly confidential and is available for review to investigator(s) and to the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB). It may not be used, divulged, published or otherwise disclosed without the written authorization from the Sponsor.

### SIGNATURE PAGE

**PROTOCOL TITLE:** A Phase 2, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate pharmacokinetics, pharmacodynamics, and safety of AT-752 in patients with dengue infection

**PROTOCOL NUMBER:** AT-02A-002

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## INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled “A Phase 2, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Trial to Evaluate Pharmacokinetics, Pharmacodynamics, and Safety of AT-752 in Patients with Dengue Infection” in accordance with the Protocol, ICH Guideline E6(R2): Good Clinical Practice and all applicable Health Authority requirements and national laws. I have read and understand all sections of the protocol.

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Investigator’s Signature

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Date

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Investigator’s Name (Please Print)

## PROTOCOL SYNOPSIS

**PROTOCOL NO.:** AT-02A-002

**TITLE:** A Phase 2 randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate pharmacokinetics, pharmacodynamics, and safety of AT-752 in patients with dengue infection

**STUDY PHASE:** 2

**STUDY SITE:** Approximately 40 sites

**INDICATION:** Dengue fever

**RATIONALE:** Dengue fever is a mosquito-borne illness that impacts an estimated 100 million people each year. There are close to 400 million infections annually, 500,000 of which develop into severe disease. Severe forms of the disease, including dengue hemorrhagic fever and dengue shock syndrome, cause significant morbidity and mortality worldwide. The disease is now endemic in over 100 countries, and its global prevalence continues to grow. Dengue fever is caused by 4 distinct serotypes of ribonucleic acid (RNA) viruses (DENV-1, DENV-2, DENV-3, and DENV-4) belonging to the flavivirus genus. Although a vaccine is available, its efficacy is variable between the different viral serotypes and it is only indicated for individuals with a history of previous dengue virus (DENV) infection. There are no effective therapeutics for dengue, and treatment options are limited to supportive care such as fluid replacement and clinical monitoring. A safe and effective antiviral therapy that targets all DENV serotypes is greatly needed to reduce the global burden of this disease and meet this unmet medical need.

Atea Pharmaceuticals is developing a novel purine nucleotide prodrug, AT-752, which is designed to treat patients that have been infected with the DENV. When dissolved, AT-752 releases the freebase AT-281, which in a series of steps, is converted to the intracellular active triphosphate metabolite, AT-9010 (triphosphate of AT-273, and therefore plasma AT-273 is considered a surrogate of intracellular AT-9010).

In preclinical studies, AT-752 showed potent in vitro antiviral activity against dengue serotypes 1-4, as well as potent in vivo antiviral activity in small animal models. A first-in-human study (Protocol AT-02A-001) was completed in 65 healthy adults to investigate the safety and pharmacokinetics (PK) (with embedded food effect and PK ethnic sensitivity evaluation) of AT-752. 41 subjects received single ascending doses (SAD) and 24 subjects participated in the multiple ascending dose (MAD) portion of the study. The first-in-human study supported dose selection for the current study.

The Phase 2 study described herein will be conducted in adult patients with confirmed DENV infection and will investigate safety, PK, and pharmacodynamics (PD) in this population. The study will be conducted in several dosing cohorts to enable dose selection for subsequent trials.

**OBJECTIVES:**

The primary objective of this study is:

- To investigate the antiviral activity of AT-752 versus placebo in terms of reduction of DENV RNA from baseline in adult subjects with confirmed DENV infection.

The secondary objectives of this study include PK and safety objectives as outlined below:

The PK objective of this study is:

- To evaluate the PK of AT-752 (AT-281) and metabolites in adult subjects with confirmed DENV infection.

The safety objective of this study is:

- To evaluate safety of AT-752 versus placebo in adult subjects with confirmed DENV infection

The exploratory objectives of this study include PD objectives as outlined below:

- To describe the effect of AT-752 on viremia (viral titre), DENV nonstructural protein 1 (NS1) levels, fever, and biomarkers (See list in [Section 8.3.4](#)) compared to placebo in adult subjects with confirmed DENV infection

**STUDY DESIGN:**

This study evaluates the safety, PK, and PD of AT-752 and will enroll approximately 60 subjects that meet the inclusion/exclusion criteria. Following screening and informed consent, eligible subjects will be randomized to receive either AT-752 or matching placebo orally 3 times a day (TID) for 5 days in Cohort 1 of the study. Subsequent cohorts will receive AT-752/placebo either twice a day (BID) or TID, as described below. Randomization will be stratified by geographic region. Standard-of-care treatment, including acetaminophen, will be permitted during the study.

At screening, information including demographics, medical history (including time since illness onset), and concomitant medications will be gathered from potential subjects. Any clinical care necessary throughout the study, such as supportive care, will be at the discretion of the investigator and institutional guidelines. Subject eligibility will be confirmed at the screening visit. Randomization and the initial dosing should occur on the same day as screening, if possible. Initial dosing should occur no later than 24 hours after screening.

For TID dosing, subjects will receive doses in the morning, at mid-day, and in the evening. TID doses will be separated by approximately 8 hours. [For BID dosing, subjects will receive doses in the morning and in the evening. BID doses will be separated by approximately 12 hours.] Subjects can continue participation even if hospitalized or using mobile nursing during the study, depending on site availability and subject decision. Subjects will be discharged on Day 6 (after end of treatment) if hospitalized, and asked to return on Day 7, Day 8, and Day 14 ( $\pm 1$  day) with a final safety follow-up performed on Day 28 ( $\pm 3$  days). For clinical sites that decide to use mobile nursing, some of the subsequent visits (Days 2-5,

Days 7-8, and Day 14) may be performed at investigator discretion through mobile nursing. The Day 1, Day 6, and Day 28 visits must be conducted at the clinical site.

The dose level for Cohort 1 (750 mg TID) was determined based on review of PK and safety data from the Phase 1 healthy volunteer study (Protocol AT-02A-001). In healthy subjects, this dose was able to rapidly achieve and maintain AT-273 troughs plasma concentrations above 200 ng/mL (in vitro EC<sub>90</sub> of AT-281 against DENV-2 is 0.64 µM or approximately 200 ng/mL equivalent of AT-273) and was well-tolerated. Specific doses for Cohort 2 and Cohort 3 will be endorsed by the Safety Review Committee (SRC) after an unblinded review of the previous cohort by the SRC.

- Cohort 1: 750 mg AT-752/placebo TID for 5 days
- Cohort 2: up to 1000 mg AT-752/placebo BID or TID for 5 days
- Cohort 3: up to 1500 mg AT-752/placebo BID for 5 days

In each blinded cohort, subjects will be randomized to receive AT-752 or placebo in a 3:1 ratio. Each cohort will include 20 subjects (15 subjects receive AT-752 and 5 receive placebo).

Prior to the initiation of each cohort after Cohort 1, all safety and available PK data through at least 5 days in the current dose cohort will undergo an unblinded review by the SRC. Following each SRC review, the dose for the next cohort will be endorsed by the SRC and the cohort enrolled.

## **STUDY POPULATION:**

### **Inclusion Criteria:**

A patient must meet the following criteria to be eligible for participation in this study:

1. 18-55 years of age at time of screening
2. Fever  $\geq 38^{\circ}\text{C}$  (or feeling feverish) with onset during the previous 60 hours
3. Positive test confirming DENV on a NS1 antigen test or reverse transcription-polymerase chain reaction (RT-PCR) assay
4. Negative rapid diagnostic test results for SARS-CoV-2 and Influenza A and B
5. Body mass index (BMI) of 18 to 30 kg/m<sup>2</sup>
6. Provides written informed consent prior to initiation of any study procedures
7. Able to understand and agrees to comply with planned study procedures and be available for all study visits
8. Males and females of childbearing potential must agree to use protocol-specified methods of contraception as described in [Section 4.1.1](#)
9. Male subjects must agree to not donate sperm from the first dose through 90 days after the last dose of study drug

**Exclusion Criteria:**

A patient who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant at screening or plans to become pregnant within 90 days of screening
2. Female patient who is breastfeeding or plans to breastfeed during the study period
3. Has previously received any investigational or approved vaccine for dengue
4. Previous history of HIV, active chronic hepatitis B infection, or current hepatitis C infection (from medical history)
5. Use of any antiviral drug within 30 days or within 5 half-lives (whichever is longer) of the active drug or metabolite (for long-acting antivirals) of screening
6. Currently enrolled in or plans to participate in another clinical trial with an investigational agent or device that will be received during the study reporting period.
7. Exposure to another investigational agent within 30 days or 5 half-lives, whichever is longer, prior to study drug administration
8. Concomitant use of herbal or natural supplements (e.g. St. John's Wort, echinacea, milk thistle) or grapefruit juice. These should be discontinued at screening if the investigator feels that they can be safely discontinued or substituted for the duration of the study.
9. Patients with chronic medical conditions that put them at risk for severe dengue, including uncontrolled diabetes mellitus, severe asthma requiring oral steroids, or admission to the hospital in the previous 6 months for cardiac disease.
10. Current use of anticoagulant or antiplatelet drugs or documented medical history of bleeding disorders
11. Malabsorption syndrome or other conditions that would interfere with enteral absorption
12. Immunocompromised due to use of immunosuppressive drugs including systemic corticosteroids (inhaled or topical corticosteroids are allowed) or immunocompromised due to any current disease or condition
13. Use of P-glycoprotein (P-gp) inducers and inhibitors as described in [Section 5.6.1](#). *Note: hydroxychloroquine and amiodarone are prohibited within 3 months prior to screening and during the study.*
14. Evidence of severe dengue disease including:
  - Severe plasma leakage leading to shock or fluid accumulation with respiratory distress
  - Severe bleeding (including any subjects with hemoglobin levels <13.0g/dL in males and <11.0g/dL in females).
  - Severe organ impairment (e.g., elevated transaminases  $\geq 1,000$  IU/L, impaired consciousness, renal failure [including any subjects with creatinine clearance < 60 mL/min {Cockcroft Gault formula}], or heart impairment [including any subjects with clinically significant abnormal ECG at Screening])
15. Suspected or confirmed acute illness thought to be caused by a pathogen other than DENV

16. Confirmed or suspected SARS-CoV-2 infection or contact with patients with confirmed SARS-CoV2 infection within 7 days prior to screening
17. ALT or AST > 5x upper limit of normal (ULN) or total bilirubin > 1.5x ULN (Gilbert's syndrome is exempt), or platelet count <80,000/mm<sup>3</sup> at the time of screening
18. Has any other medical disease or condition that in the opinion of the site principal investigator or appropriate sub-investigator, precludes study participation. This includes any acute, subacute, intermittent, or chronic disease or condition that would place the patient at an unacceptable risk of injury, render the patient unable to meet the requirements of the protocol, or interfere with the evaluation of responses or the patient's successful completion of the trial

**ESTIMATED STUDY DURATION:**

Subject participation in this study will be up to 32 days. After screening (within 60 hours of onset of a fever), each subject will receive the investigational drug or placebo on Day 1 and should continue on the regimen-specific schedule until all planned doses are completed (10 doses for BID dosing and 15 doses for TID dosing). If possible, screening and Day 1 visits should occur on the same day. After dosing is complete (on Day 5 or Day 6 depending on what time of day dosing starts on Day 1), subjects will have additional assessments on Days 6-8 and will have follow-up visits on Days 14 ( $\pm$  1 day) and 28 ( $\pm$  3 days). The maximum duration that any patient will be involved is 32 days (screening day plus 28 - 31 days from beginning of treatment to end of follow-up).

**STUDY PROCEDURES:****Primary Endpoint**

- Change in DENV viral load (DENV RNA as measured by RT-qPCR) from baseline

**Secondary Endpoints: PK Endpoints**

Pharmacokinetic endpoints will be characterized as subject numbers and PK data permit.

- Plasma concentrations of AT-281 (and metabolites AT-551, AT-229, AT-219 and AT-273) for each cohort at:
  - Day 1 at time 0 (pre-dose; before the first dose on Day 1)
  - 24 hours after Dose 1 (before Dose 4 for TID dosing and before Dose 3 for BID dosing)
  - A day of intensive PK sampling:
    - For TID dosing, samples will be obtained before Dose 7 and 0.5, 1, 2, 4, and 6 hours after Dose 7. This serial PK sampling may be done for Dose 7, 8, or 9, based on site/patient convenience
    - For BID dosing, samples will be obtained before Dose 5 and 0.5, 1, 2, 4, 6, and 8 hours after Dose 5. This serial PK sampling may be done for Dose 5, 6, or 7, based on site/patient convenience



For blood samples (both TID and BID dosing), a  $\pm 10$  minutes window for time points  $\leq 4$  hours;  $\pm 15$  minute for time points between 4 and 24 hours

- At any early study discontinuation visit: The timing of these PK samples relative to the last 2 (most recent) doses will be recorded
- Noncompartmental analysis will be performed for the following plasma PK parameters, when applicable and if data permit. Other PK parameters may also be calculated. PK parameters, where applicable, will be calculated based on actual times:
  - $AUC_{last}$  (area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration)
  - $AUC_{tau}$  (area under the plasma concentration versus time curve over the dosing interval)
  - $AUC_{inf}$  (area under the plasma concentration versus time curve from time 0 to extrapolated to infinity)
  - $C_{max}$  (maximum observed plasma concentration)
  - $T_{max}$  (time to maximum observed plasma concentration)
  - $t_{1/2z}$  (apparent terminal elimination half-life)
  - CL/F (apparent oral clearance)
  - $V_z/F$  (apparent volume of distribution)
  - $C_{trough}$  (trough concentration)

#### **Secondary Endpoints: Safety Endpoints**

- Incidence and grade of any treatment-emergent adverse events (TEAEs) from first dose through Day 28 or withdrawal from the study
- Incidence and grade of any serious adverse events (SAEs) through Day 28 or withdrawal from the study
- Vital sign measurements
- Physical examination findings
- Clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) findings
- Electrocardiogram (ECG) findings

#### **Exploratory Endpoints: PD Endpoints**

- Change in DENV viral load (as measured by infectious viral titre) from baseline
- Area under the log10-transformed viral load curve (AUC) from first dose to the end of treatment or study (as measured by DENV RNA and viral titre)

- Time to viral load clearance, which is defined as the first of 2 consecutive undetectable viral load measurements [as measured by DENV RNA and viral titre]
- Time to clearance of NS1 protein using a NS1 antigen test. Clearance is defined as time from start of treatment until the first of 2 consecutive plasma samples are NS1-negative.
- Change of DENV viral load (as measured by DENV RNA and viral titre) from baseline, viral load AUC, time to viral load or NS1 clearance by DENV serotype
- Treatment-emergent amino acid substitutions in DENV NS5 polymerase
- Time to resolution or duration of fever
- Exploratory biomarkers on immunological response to dengue (See list in [Section 8.3.4](#))
- Exploratory analyses may be performed to evaluate exposure-response relationship. The relationship between the exposure of AT-752 (and its metabolites) and DENV viral load may be explored using graphical displays

#### STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:

Dose levels of AT-752 will be evaluated across 3 sequential cohorts dosed orally:

- Cohort 1: 750 mg AT-752/placebo TID for 5 days
- Cohort 2: up to 1000 mg AT-752/placebo BID or TID for 5 days
- Cohort 3: up to 1500 mg AT-752/placebo BID for 5 days

#### STATISTICAL ANALYSIS PLANS:

##### Sample Size:

In Low et al ([Low 2014](#)), the observed standard deviations (SD) for VLR, defined as mean change from baseline viral load on days 2, 3, and 4, ranged from 0.75 (N=26) to 1.07 (N=24). Taking into account that the VLR endpoint in that study was based on an average of 3 measurements and assuming that there is some correlation between measurements on days 2 through 4, we consider power to detect a true effect at a single time point using a one-sided 0.10 level test (unadjusted for multiple comparisons) with N=15 per arm for SD in a range from 1 to 1.75:

True standard deviation	Effect (log 10 copies/ml) with 80% power (N=15 vs. 15) Comparison versus placebo pooled across 3 planned cohorts	Effect (log 10 copies/ml) with 80% power (N=15 vs. 5) Comparison versus placebo within a cohort
1	0.8	1.1
1.25	1	1.4
1.5	1.2	1.7
1.75	1.4	2.0

Based on the above table, there is 80% power to detect a true treatment effect (versus placebo) on change-from-baseline viral load of 1 log<sub>10</sub> at a time point if the true SD is 1.25 for comparison of groups with N=15 each. The analogous power to detect a 1 log<sub>10</sub> effect for a within cohort comparison is 59%. Furthermore, if true SD is in the range from 1 to 1.75, the probability that the observed effect would be 0.5 log<sub>10</sub> or larger is low (in range from 0.09 to 0.22) if there is no treatment effect, i.e., an observed effect of 0.5 or larger might be considered suggestive of a signal. Interpretation of results will consider the totality of the data.

**Statistical Methods:**

The primary objective of this study is to investigate the antiviral activity of AT-752 versus placebo in terms of reduction of DENV RNA from baseline.

Change from baseline in viral load based on the log<sub>10</sub> scale will be compared between each AT-752 arm and a combined placebo group at specific timepoints. Viral load will be analyzed using repeated measures mixed model with treatment, time, and treatment-by-time interaction as fixed factors. The treatment group least squares mean (LSM) estimates for mean change from baseline and treatment group differences at a time point, with 80% confidence interval (CI) and p-value will be presented. Additionally, descriptive summaries for the change from baseline will also be presented by treatment group. Further details will be provided in a separate statistical analysis plan (SAP).

Safety, PK, and PD data will be summarized in tabular and/or graphical format by active dose treatment arms and a pooled placebo arm. Continuous data will be summarized using descriptive statistics (n, mean, SD, median, 95% CI) and categorical data will be summarized using counts and percentages. All subject-level data will be presented in listings.

The primary analysis population is the modified intent-to-treat (mITT) population, which will include all randomized subjects who received at least 1 dose of study drug and have baseline and at least 1 post-baseline virology measurement. The primary analysis will also be performed on the per-protocol population of patients who completed treatment without a major protocol deviation. The population for PK analysis will include subjects who receive at least 1 dose of the study drug and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. The safety population will include all subjects who receive at least 1 dose of the study drug. The population for PD analysis will be the mITT population. A per protocol population will include the subset of the modified intent-to-treat population who completed study drug treatment without a major protocol violation.

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**1. BACKGROUND**

**1.1 DENGUE VIRUS**

Flaviviruses are single-stranded, positive-sense ribonucleic acid (RNA) viruses. Medically important mosquito -borne flaviviruses include dengue virus (DENV), West Nile virus, Japanese encephalitis virus, yellow fever virus, and Zika virus. Among these viruses, DENV produces the highest incidence of illness, with an estimated 400 million infections each year, of which approximately 100 million with clinical manifestations, including dengue hemorrhagic fever and about 25 000 deaths (CDC2020, WHO 2020, Low 2018). The recent decades have witnessed a drastic resurgence of DENV with over 8-fold increase of dengue cases reported to the World Health Organization (WHO) in the past 20 years (WHO 2020) with large outbreaks, while mostly in tropical and sub-tropical regions including Africa, Southeast Asia, and South America, also occurred in parts of Europe (Wilder-Smith 2012). Dengue is now endemic in more than 100 countries/regions worldwide (Low 2018). Dengue fever is also on the rise in United States with over 5000 cases, mostly travel-associated, reported between 2010 and 2017 (Rivera 2020).

There are 4 antigenically distinct but closely related DENV serotypes (DENV 1-4). Isolation of a fifth serotype (DENV-5) was reported in 2013, although it has yet to be officially recognized. Recovery from infection is believed to provide lifelong immunity against that specific serotype. However, cross-immunity to the other serotypes after recovery is only partial and transient. Secondary infection by other serotypes increases the risk of developing severe dengue ([WHO 2020](#)).

There are no direct-acting antivirals (DAAs) or broadly indicated vaccines approved for DENV. The only licensed vaccine (Dengvaxia<sup>®</sup>) has a restricted indication only for individuals who have had at least one documented previous DENV infection. Moreover, protection by Dengvaxia against DENV is not complete with an efficacy of approximately 80% ([Dengvaxia 2020](#)). Efficacy is variable for each of the 4 DENV serotypes and appears to quickly wane ([Thomas 2017](#)). Therefore, in view of the global re-emergence of DENV, in addition to vaccines, parallel efforts have to be urgently devoted to developing effective DAAs to treat DENV infection.

The viral replication cycle offers multiple targets for DAAs. Among those targets, viral polymerase, a critical enzyme in viral replication, has proven to be a valid target for RNA and deoxyribonucleic acid (DNA) viruses including among others hepatitis B virus, hepatitis C virus, and human immunodeficiency virus-1 (HIV). Many nucleoside/nucleotides viral polymerase inhibitors have successfully been developed and become a cornerstone in treating major human viral diseases.

The virus' nonstructural protein 5 is the largest nonstructural protein and functions as the viral RNA-dependent RNA polymerase (RdRp). The highly conserved nature of DENV RdRp potentially allows for a single agent to be active against all viral serotypes. Similarly, to other viruses, the DENV RdRp has been the target of many investigational DAAs, mostly nucleoside/nucleotide analogues as expected ([Troost 2020](#)). Yet, to date, only one nucleoside analogue, balapiravir, has been tested clinically; however, it showed no difference between active and placebo regarding antiviral response, cytokine profile, and time to fever clearance ([Nguyen 2012](#)).

## 1.2 AT-752

Atea Pharmaceuticals, Inc. is developing AT-752, an orally administered guanosine nucleotide prodrug with potent inhibitory activity against the replication of DENV *in vitro* and *in vivo* in preclinical evaluations. A comprehensive non-clinical program and data



package, including chronic 14-day repeat-dose Good Laboratory Practice toxicology studies in 2 species (rat and monkey), was completed to support clinical studies in human subjects.

AT-752 is the hemisulfate salt of AT-281, a phosphoramidate prodrug, which undergoes multistep activation to the intracellular active 5'-triphosphate metabolite (AT-9010) of the nucleoside 2'-fluoro-2'-C-methylguanosine (AT-273).

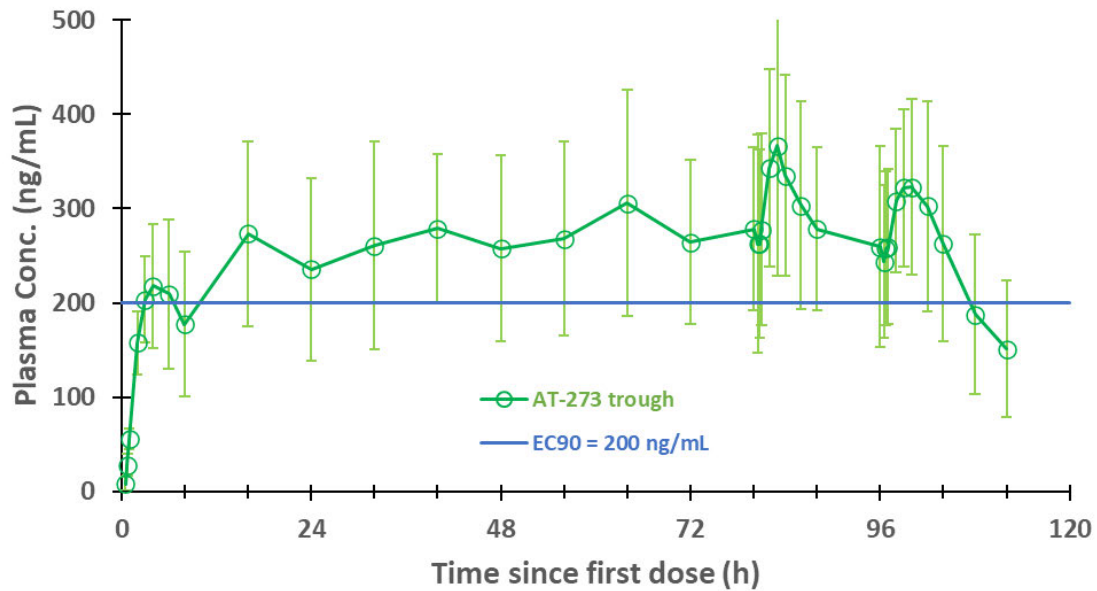
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Further information on the study drug can be found in the investigator's brochure ([Atea Pharmaceuticals](#)).

### 1.2.1 Clinical Studies

A first-in-human, randomized, double-blind, placebo-controlled study (Protocol AT-02A-001) was conducted in 65 healthy adults to investigate the safety, tolerability, and PK of AT-752. Single doses up to 1500 mg and multiple doses (1000 mg QD x 7 days; 750 mg BID x 4.5 days; 750 mg BID x 4.3 days) were evaluated. Based on the human PK results obtained from this study, an AT-752 dose of 750 mg TID (starting dose for the current study) is anticipated to demonstrate antiviral activity in dengue patients. In healthy subjects, this regimen rapidly achieved plasma concentrations of AT-273, considered plasma surrogate for the intracellular active triphosphate metabolite AT-9010, in excess of 200 ng/mL (in vitro EC<sub>90</sub> of AT-281 against DENV-2 is 0.64 μM or approximately 200 ng/mL equivalent of AT-273) and maintained through concentrations consistently above this threshold throughout the treatment duration ([Figure 1-2](#)).

**Figure 1-1 Mean (+SD) Plasma Concentration-Time Profile of AT-273, Surrogate of the Intracellular Active Triphosphate Metabolite AT-9010, Following Oral Administration of 750 Mg TID of AT-752 Under Fasted Conditions in Healthy Participants (AT-02A-001 Cohort 3b; N=6)**



Furthermore, a high-fat/high-calorie meal did not impact the total exposure of AT-281 while slightly increasing plasma exposure of AT-273. Therefore, AT-752 can be dosed without or with a meal. Also, plasma exposure of AT-273 was similar between a separately enrolled ethnic cohort of healthy participants with southeast Asian origins and the general population (Cohort 3a), whereas plasma exposure of AT-281, AT-551, and AT-229 was numerically higher by 20-30%, which is within the expected variability for the drug. Dose adjustment is not expected for this ethnic group.

AT-752 was well tolerated after either single or multiple doses in healthy subjects. Other than a single subject who withdrew consent, all other subjects completed the study. There were no SAEs reported. Most AEs were Grade 1 (mild) in intensity and no AEs of  $\geq$  Grade 3 severity were reported. The most common AEs across both parts of the study were headache, nausea, and vomiting. GI-related events (e.g., nausea, vomiting, abdominal pain, diarrhea, and constipation) were observed more commonly with AT-752 as compared to placebo. Vomiting appeared to increase with increasing AT-752 dose level ( $\geq$ 750 mg), although cases were mild/moderate in intensity and were self-limiting or managed with ondansetron. Most changes in laboratory parameters were mild (Grade 1) with no apparent relationship between

the incidence of any laboratory toxicity and AT-752 dose level. Clinically significant changes were not reported for ECG parameters.

Additional details on this study can be found in the investigator's brochure v 2.0 ([Atea Pharmaceuticals](#)).

### **1.3 RATIONALE FOR STUDY**

Dengue is caused by 4 distinct types of RNA viruses (DENV-1, DENV-2, DENV-3, and DENV-4) belonging to the flavivirus genus. Although a vaccine is available, its efficacy is variable between the different serotypes and it is only indicated for individuals with a history of previous DENV infection. There are no effective therapeutics for dengue, and treatment options are limited to supportive care such as fluid replacement and clinical monitoring. A safe and effective antiviral therapy that targets all DENV serotypes is greatly needed to reduce the global burden of this disease and meet this unmet medical need.

Atea Pharmaceuticals is developing a novel purine nucleotide prodrug, AT-752, which is designed to treat patients that have been infected with the DENV. Supported by tolerability/safety and PK in healthy subjects (see [Section 1.2.1](#)), the next logical development step for a dengue treatment is to evaluate safety, antiviral activity and PK/PD relationships of differing doses of AT-752 in DENV-infected patients. This study will evaluate the safety, PK, and PD of AT-752 in adult patients with confirmed DENV infection and further support dose selection for subsequent, later phase trials.

### **1.4 RATIONALE FOR DOSE SELECTION**

The dose levels selected for the study described herein are:

- Cohort 1: 750 mg AT-752/placebo 3 times a day (TID) for 5 days
- Cohort 2: up to 1000 mg AT-752/placebo twice a day (BID) or TID for 5 days
- Cohort 3: up to 1500 mg AT-752/placebo BID for 5 days

Based on the PK results of the AT-02A-001 study (see [Section 1.2.1](#)), the AT-752 starting dose of 750 mg TID (2250 mg total daily dose) is anticipated to demonstrate antiviral activity in dengue patients. This dose rapidly achieved and maintained plasma AT-273 troughs above the target 200 ng/mL (in vitro EC<sub>90</sub> of AT-281 against DENV-2 is 0.64 µM or approximately

200 ng/mL equivalent of AT-273). Starting from the second dose, 75% of individual AT-273 troughs were above this threshold.

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## **2. STUDY OBJECTIVES**

The primary objective of this study is:

- To investigate the antiviral activity of AT-752 versus placebo in terms of reduction of DENV RNA from baseline in adult subjects with confirmed DENV infection

The secondary objectives of this study include PK and safety objectives as outlined below.

The PK objective of this study is:

- To evaluate the PK of AT-752 (AT-281) and metabolites in adult subjects with confirmed DENV infection.

The safety objective of this study is:

- To evaluate safety of AT-752 versus placebo in adult subjects with confirmed DENV infection

The exploratory objectives of this study include PD objectives as outlined below:

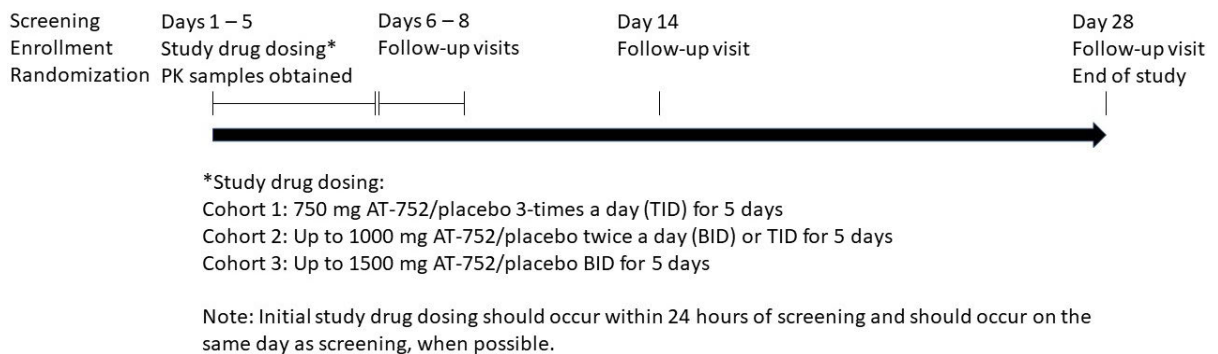
- To describe the effect of AT-752 on viremia (viral titre), DENV nonstructural protein 1 (NS1) levels, fever, and biomarkers (see list in [Section 8.3.4](#)) compared to placebo in adult subjects with confirmed DENV infection

### 3. STUDY DESIGN

This study evaluates the safety, PK, and PD of AT-752 will enroll approximately 60 subjects that meet the inclusion/exclusion criteria. Following screening and informed consent, eligible subjects will be randomized to receive either AT-752 or matching placebo orally TID for 5 days in Cohort 1 of the study. Subsequent cohorts will receive AT-752/placebo either BID or TID, as described in [Figure 3-1](#). Randomization will be stratified by geographic region. Standard-of-care treatment, including acetaminophen, will be permitted during the study.

A schematic of the study design is provided in [Figure 3-1](#).

**Figure 3-1 AT-02A-002 Study design**



At screening, information including demographics, medical history (including time since illness onset), and concomitant medications will be gathered from potential subjects. Additional assessments and collection of data will be conducted as indicated in the schedule of events (SOE; [Table 3-1](#)). Any clinical care necessary throughout the study, such as supportive care, will be at the discretion of the investigator and institutional guidelines. After subjects are confirmed eligible at screening, randomization and the initial dosing should

occur within 24 hours, and if possible, the initial dose should be given on the same day as screening.

Upon randomization, subjects will receive their first dose of study drug. Subjects in Cohort 1 will receive doses that are separated by approximately 8 hours ( $\pm 2$  hours; morning, mid-day, and evening). [Subjects receiving BID dosing will receive doses that are separated by 12 hours ( $\pm 2$  hours; morning and evening)]. Subjects can continue participation even if hospitalized or using mobile nursing during the study, depending on site availability and subject decision. Subjects will be discharged on Day 6 (after end of treatment) if hospitalized, and asked to return on Day 7, Day 8, and Day 14 ( $\pm 1$  day) with a final safety follow-up performed on Day 28 ( $\pm 3$  days). For clinical sites that decide to use mobile nursing, some of the subsequent visits (Days 2-5, Days 7-8, and Day 14) may be performed at investigator discretion through mobile nursing. The Day 1, Day 6, and Day 28 visits must be conducted at the clinical site. The Day 6 end of treatment visit will occur 8 to 24 hours after the last dose of study medication is administered.

Note that if the initial dose of study drug is administered on the same day as screening (at mid-day or in the evening), the last dose of study drug will be administered on Day 6. See [Section 3.1.2](#) and [Section 3.1.3](#) for detailed descriptions of TID and BID dosing, respectively.

The 3 planned sequential dosing cohorts are:

- Cohort 1: 750 mg AT-752/placebo TID for 5 days
- Cohort 2: up to 1000 mg AT-752/placebo BID or TID for 5 days
- Cohort 3: up to 1500 mg AT-752/placebo BID for 5 days

In each blinded cohort, subjects will be randomized to receive active drug or placebo in a 3:1 randomization. Each cohort will include 20 subjects (15 subjects receive AT-752 and 5 subjects receive placebo).

Specific doses for Cohort 2 and Cohort 3 will be endorsed by the SRC) after an unblinded review of the previous cohort by the SRC. Prior to the initiation of each cohort after Cohort 1, all safety and available PK data through at least 5 days in the current dose cohort will undergo an unblinded review by the SRC. Following each SRC review, the dose for the next cohort will be endorsed by the SRC and the cohort enrolled according to schedule outlined in the SOE ([Table 3-1](#)).

### 3.1 SCHEDULE OF ASSESSMENTS

**Table 3-1 Schedule of Events**

Assessment	Screening	Treatment Period			Follow-up				
		Day 1	Days 2-4	Day 5	Day 6	Day 7	Day 8	Day 14±1	Day 28 ±3/ EOS (Early Termination)
Visit Type	Site	Site	Site or Mobile	Site or Mobile	Site	Site or Mobile	Site or Mobile	Site or Mobile	Site
Eligibility criteria	X								
Informed consent <sup>a</sup>	X								
Demographics	X								
Medical history	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination <sup>b</sup>	X	X	X	X	X	X	X	X	X
Vital signs <sup>c</sup>	X	X	X	X	X				
12-lead ECG (triplicate-consecutive)	X				X				X
Chemistry/hematology/coagulation <sup>d</sup>	X	X	Day 2, 4		X		X	X	X
Urinalysis w/ microscopy <sup>d</sup>	X	X			X		X		
SARS-CoV-2 rapid test, RIDT <sup>e</sup>	X				X				
Pregnancy testing <sup>f</sup>	X								
NS1 rapid test <sup>g</sup>	X								
Pharmacokinetic assessments <sup>h</sup>		X	Day 2 and Day 3 or 4						
DENV serotype testing <sup>i</sup>	X								
Viral load <sup>j</sup>	X	X	X	X	X	X	X	X	X (Day 28 only)
NS1 antigen test	X	X	X	X	X	X	X	X	X (Day 28 only)



Plasma Biomarker	X	X	Day 2, 4		X		X	X	X (Day 28 only)
Adverse events <sup>k</sup>	X	X	X	X	X	X	X	X	X
Randomization	Prior to dosing								
Study drug administration		X	X	X					
Accountability of returned drug, and review of patient diary					X				X (Early Termination only)

Abbreviations: DENV = dengue virus; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; NS1 = nonstructural protein 1; RIDT = rapid influenza diagnostic test

- a. Informed consent will be performed before any study procedures are conducted. Results from standard of care evaluations that are available prior to informed consent are accepted if performed within 24 hours of screening
- b. A full physical examination, including height and weight, will be performed at screening and Day 28, except height will not be collected at Day 28. Symptom-directed physical examinations will be performed at the remaining visits.
- c. On Day 1, vital signs should be collected pre-administration of study drug. Vital sign measurements should be performed before any scheduled blood collections. On subsequent days (Days 2-6), vital signs can be collected at any time.  
In addition, temperature readings will be performed at least 4 times daily, in the morning, mid-day, late afternoon, and evening (approximately every 4 hours while the subject is awake) through the end of treatment. Temperature will be measured orally and will be recorded in a patient diary (and given to the site coordinator for entry in the eCRF).
- d. Hematology/ chemistry/ coagulation to include complete blood count (CBC) including white blood cell (WBC) count with differential count, red blood cell (RBC) count, platelet count, hemoglobin, hematocrit, and RBC indices; aspartate transaminase (AST), alanine aminotransferase (ALT), total and direct bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, serum creatine kinase, lipase, bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, total protein, albumin, phosphate, calcium, and amylase; international normalized ratio (INR), prothrombin time, and partial thromboplastin time. Urinalysis will be performed with microscopy at indicated visits but treatment with study drug may begin before the screening results have been obtained unless medically required to establish eligibility (at investigator's discretion). Additional urinalysis may be performed as clinically indicated.  
One-time retests of individual screening laboratory parameters or assessments may be permitted in certain scenarios. Such scenarios may include lab processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting screening laboratory results. Standard of care laboratory results prior to informed consent are accepted if performed within 24 hours of screening.
- e. SARS-CoV-2 rapid test performed at screening and Day 6. RIDT performed only at screening.
- f. A dipstick pregnancy test is required at screening. Additional pregnancy tests may be performed locally as clinically indicated.
- g. Rapid point of care (POC) test for DENV NS1 antigen. See [Section 3.1.4](#) for details about assay timing.
- h. Pharmacokinetic (PK) plasma samples will be collected on Day 1 at time 0 (pre-dose; before the first dose on Day 1) and 24 hours after Dose 1. For TID dosing, samples will be obtained before Dose 7 and 0.5, 1, 2, 4, and 6 hours after Dose 7. This serial PK sampling for TID dosing may be done for Dose 7, 8, or 9, based on site/patient convenience. For BID dosing, samples will be obtained before Dose 5 and 0.5, 1, 2, 4, 6, and 8 hours after Dose 5. This serial PK sampling for BID dosing may be done for Dose 5, 6, or 7, based on site/patient convenience. For blood samples, a ± 10-minute window for time points ≤4 hours; ± 15 minute for time points between 4 and 24 hours. PK samples will also be obtained at any early study discontinuation visits. The timing of these PK samples relative to the last 2 (most recent) doses will be recorded. See [Section 3.1.4](#).
- i. Subjects can begin treatment with study drug before the DENV-serotype results are obtained.

- 
- j. Measurement of plasma viremia by viral titre and using a serotype-specific, real-time reverse transcription polymerase chain reaction (RT-PCR) assay. Subjects can begin treatment before the viral load results are obtained. See [Section 3.1.4](#) for details about the timing of this assay.
- k. Adverse events are collected beginning at screening. Treatment-emergent adverse events and serious adverse events will be assessed from the time of study drug dosing until end of study and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.
- l. After subjects are confirmed eligible at screening, randomization and the initial dosing should occur within 24 hours, the initial dose should be given on the same day as screening, if possible. TID dosing at screening/Day 1 can begin in the morning, at mid-day, or in the evening (see [Section 3.1.2](#). BID dosing on Screening/Day 1 can begin in the morning or the evening (See [Section 3.1.3](#)).  
Note that if the initial dose of study drug is administered on the same day as screening (at mid-day or in the evening), the last dose(s) of study drug will be administered on Day 6.
- 

### 3.1.1 Screening/Day 1

After eligibility is determined at screening, the initial dose of study drug can be administered after randomization and within 24 hours of screening. This can occur before obtaining the results of the DENV serotype testing and viral load assessments. If possible, administer the initial dose of study drug on the same day as screening.

Evaluations that must be completed before administering the initial dose include:

- Determining eligibility criteria
- Obtaining informed consent
- Recording demographics, medical history, and concomitant medications
- Complete physical examination. If the initial dose of study drug is administered on the same day as screening, the results of the complete physical examination at screening will be substituted for symptom-directed physical examination on Day 1
- Vital signs. On Day 1, vital sign measurements should be performed before any scheduled blood collections and prior to administration of study drug. If the initial dose of study drug is administered on the same day as screening, the results of the vital signs obtained at screening will be used for the Day 1 vital sign results. Note that oral temperature is also to be collected during the dosing period at least 4 times a day (morning, mid-day, late afternoon, evening; approximately every 4 hours while subjects are awake)
- Triplicate consecutive 12-lead ECG.

- Chemistry, hematology, coagulation, and urinalysis (with microscopy). At screening, samples should be collected for urinalysis (with microscopy), but subjects can begin treatment with study drug before the results are obtained unless medically required to establish eligibility (at investigator's discretion). If the initial dose of study drug is administered on the same day as screening, the screening results for these tests will be used for the Day 1 results. Results from standard-of-care evaluations that are available prior to informed consent are accepted if performed within 24 hours of screening
- SARS-CoV-2 rapid test, rapid influenza diagnostic test, and urine pregnancy testing
- DENV serotype testing. Subjects can begin treatment with study drug before the DENV-serotype results are obtained, but the samples should be obtained before dosing
- Viral load. Measurement of plasma viremia by viral titre and using a serotype-specific, real-time RT-PCR assay. Subjects can begin treatment with study drug before the DENV-serotype results are obtained, but the sample should be obtained prior to dosing. If the initial dose of study drug is administered on the same day as screening, the screening results for viral load will be used for the Day 1 values
- NS1 antigen detection test. If the initial dose of study drug is administered on the same day as screening, the screening results for NS1 antigen will be used for the Day 1 values
- Adverse events. AEs will be collected from screening to end of study (EOS)
- Randomization. Randomization will be stratified by geographic region

### **3.1.2 Timing of TID Dosing**

If possible, the first dose of study medication should be administered on the same day as screening.

The first dose of study medication (on Day 1) must be taken under observation at the study site. All other doses will be administered at the study site for subjects who are confined to the site during the study, or will be self-administered outside the study site (e.g., at home) for subjects at sites that choose to use mobile nursing (except the doses administered prior to PK evaluation [Dose 7, 8, or 9; see [Section 3.1.4](#)], which must be taken under observation at

the study site, or under observation by mobile nursing staff as applicable). The timing of the doses will be recorded in a patient diary.

The first dose of study medication should be administered between 6 AM and 4 PM, inclusive or between 8 PM and 10 PM, inclusive. Dosing after 4 PM but before 8 PM would make scheduling for the second dose difficult, considering the later hours.

The second dose of study medication must be taken after at least 6 hours and no later than 10 hours after the first dose, allowing the participant to select a convenient 8-hour ( $\pm 2$  hours) dosing schedule thereafter to complete a total of 15 doses.

For example, if a patient intends to choose a 6 AM, 2 PM, 10 PM dosing schedule:

- Then if the first dose is administered between 6 AM and 8 AM on Day 1, the second dose should be administered at 2 PM on Day 1 and the third dose at 10 PM on Day 1, and the subject can then proceed with the 6 AM, 2 PM, and 10 PM dosing schedule on Day 2 and thereafter.
- Or if the first dose is administered between 8 AM and 10 AM on Day 1, the second dose should be administered at 4 PM on Day 1 and the third dose at 10 PM on Day 1, and the subject can then proceed with the 6 AM, 2 PM, and 10 PM dosing schedule on Day 2 and thereafter.
- Or if the first dose is administered between 10 AM and noon on Day 1, then the second dose should be administered at 8 PM on Day 1, and the subject can then proceed with the 6 AM, 2 PM, and 10 PM dosing schedule on Day 2 and thereafter.
- Or if the first dose is administered between noon and 4 PM on Day 1, the second dose should be administered at 10 PM on Day 1, and the subject can then proceed with the 6 AM, 2 PM, and 10 PM dosing schedule on Day 2 and thereafter.
- Or if the first dose is administered between 8 PM and 10 PM on Day 1, the subject can then proceed with the 6 AM, 2 PM, and 10 PM dosing schedule on Day 2 and thereafter.

Doses of AT-752 and matching placebo should be separated by 8 hours ( $\pm 2$  hours). After Day 1, if a dose is delayed, it should be taken as soon as possible, but must be taken at least 6 hours before the next scheduled dose. Otherwise, the dose must be skipped, and the next dose

taken as scheduled. Dosing will be stopped at the end of the 15-dose treatment period. At the end of the treatment period, the tablets from any missed doses should be returned to the site.

Treatment adherence will be assessed by a study medication log (patient diary), which will be completed by the clinic staff for in clinic doses and by the participant for out of clinic doses.

### **3.1.3 Timing of BID Dosing**

If possible, the first dose of study medication should be administered on the same day as screening.

The first dose of study medication (on Day 1) must be taken under observation at the study site. The doses for PK evaluation (for Dose 5, 6, or 7; see Section 3.1.4) must also be taken under observation at the study site, or under observation by mobile nursing staff as applicable.

All other doses may be administered either at the study site or will be self-administered outside the study site (e.g., at home). The timing of the doses will be recorded in a patient diary.

The second dose of study medication must be taken after at least 6 hours and no later than 12 hours after the first dose, allowing the participant to select a convenient 12-hour ( $\pm 2$  hours) dosing schedule thereafter to complete a total of 10 doses. For example,

- If the first dose of study medication is administered between 6AM and 1 PM on Day 1, the second dose should be administered between 6 PM and no later than 10PM on Day 1, and then the subject can begin their preferred 12-hour dosing schedule on Day 2 (e.g., 6 AM and 6 PM, OR 7 AM and 7 PM, OR 8 AM or 8 PM, etc.), as long as the 12 hours ( $\pm 2$  hours) timing of doses is adhered to.
- Or if the first dose of study medication is administered between 1 PM and 4 PM on Day 1, the second dose should be administered at 10 PM on Day 1, and then the subject can begin their preferred 12-hour dosing schedule on Day 2 (eg, 6 AM and 6 PM, OR 7 AM and 7 PM, OR 8 AM or 8 PM, etc), as long as the 12 hours ( $\pm 2$  hours) timing of doses is adhered to.
- Or if the first dose of study medication is administered between 6 PM and 10 PM on Day 1, the subject can then begin their preferred 12-hour dosing schedule on Day 2

(e.g., 6 AM and 6 PM, OR 7 AM and 7 PM, OR 8 AM or 8 PM, etc.), as long as the 12 hours ( $\pm 2$  hours) timing of doses is adhered to.

Doses of study drug should be separated by 12 hours ( $\pm 2$  hours). After Day 1, if a dose is delayed, it should be taken as soon as possible, but must be taken at least 6 hours before the next scheduled dose. Otherwise, the dose must be skipped, and the next dose taken as scheduled. Dosing will be stopped at the end of the 10-dose treatment period. At the end of the treatment period, the tablets from any missed doses should be returned to the site.

Treatment adherence will be assessed by a study medication log (patient diary), which will be completed by the clinic staff for in clinic doses and by the participant for out of clinic doses.

### **3.1.4 Timing of Samples for PK, Viral Load, and NS1**

The timing of samples for PK analyses, viral load determination, and NS1 levels are outlined below for TID and for BID dosing. As shown in the tables below, the timing will vary depending on the time of day that the patient received Dose 1 of study medication and how many doses of study medication they received on Day 1.

10. Timing of sample collections for patients who begin TID dosing at different times on Day 1 and thus receive either 3 doses, 2 doses, or 1 dose of study medication on Day 1, are provided in [Table 3-2](#), [Table 3-3](#), and [Table 3-4](#), respectively. In these tables, Day 1 is the day of dosing. Some of the PK sample times are fixed (pre-dose on Day 1, 24 hours after Dose 1), and some are flexible (serial PK samples for TID dosing may be obtained at either dose 7, 8, or 9). Some of the virology sample times are fixed (pre-dose on Day 1, 24 hours after Dose 1, 48 hours after Dose 1, and 8-24 hours after Dose 15). Other virology sample times are flexible, with samples collected anytime on each of 6 days (Days 4, 5, 7, 8, 14, and 28).
11. Timing of sample collections for patients who begin BID dosing at different times on Day 1 and thus receive either 2 doses or 1 dose of study medication on Day 1, are provided in [Table 3-5](#) and [Table 3-6](#), respectively. In these tables, Day 1 is the day of dosing. Some of the PK sample times are fixed (pre-dose on Day 1, 24 hours after Dose 1), and some are flexible (serial PK samples for BID dosing may be obtained at either dose 5, 6, or 7). Some of the virology sample times are fixed (pre-dose on Day 1, 24 hours after Dose 1, 48 hours after Dose 1, and 8-24 hours after Dose 10). Other virology sample times are flexible, with samples collected anytime on each of 6 days (Days 4, 5, 7, 8, 14, and 28).

**Table 3-2 TID dosing beginning before 10 AM, with 3 doses given on Day 1: Timing of samples for PK, viral load, and NS1**

For TID Dosing (with 3 doses given on Day 1)			
Day	Dose #	PK draw	Viral load and NS1
Day 1	1	Predose	Predose
	2		
	3		
Day 2	4	24 hrs post Dose #1	24 hrs post Dose #1 (prior to Dose #4)
	5		
	6		
Day 3	7	Predose #7 AND 0.5, 1, 2, 4, and 6 hrs post dose #7  NOTE: Serial PK can be done at Dose 7, 8, or 9 (based on site/patient convenience).	48 hrs post Dose #1 (prior to Dose #7)
	8		
	9		
Day 4	10		One sample anytime Day 4
	11		
	12		
Day 5	13		One sample anytime Day 5
	14		
	15		
Day 6			8-24 hrs post Dose #15
Day 7			Any time
Day 8			Any time
Day 14			Any time
Day 28			Any time

**Table 3-3 TID dosing beginning between 10 AM and 4 PM, with 2 doses given on Day 1: Timing of samples for PK, viral load, and NS1**

For TID Dosing (with 2 doses given on Day 1)			
Day	Dose #	PK draw	Viral load and NS1
Day 1	1	Predose	Predose
	2		
Day 2	3	24 hrs post Dose #1 (prior to Dose #4)	24 hrs post Dose #1 (prior to Dose #4)
	4		
	5		
Day 3	6	Predose #7 AND 0.5, 1, 2, 4, and 6 hrs post dose #7  NOTE: Serial PK can be done at Dose 7, 8, or 9 (based on site/patient convenience).	48 hrs post Dose #1 (prior to Dose #7)
	7		
	8		
Day 4	9		One sample anytime Day 4
	10		
	11		
Day 5	12		One sample anytime Day 5
	13		
	14		
Day 6	15		8-24 hrs post Dose #15
Day 7			Any time
Day 8			Any time
Day 14			Any time
Day 28			Any time



**Table 3-4 TID dosing beginning in the evening, with 1 dose given on Day 1:  
 Timing of samples for PK, viral load, and NS1**

For TID Dosing (with 1 dose given on Day 1)			
Day	Dose #	PK draw	Viral load and NS1
Day 1	1	Predose	Predose
Day 2	2		
	3		
	4	24 hrs post Dose #1 (prior to Dose #4)	24 hrs post Dose #1 (prior to Dose #4)
Day 3	5		
	6		
	7	Predose #7 AND 0.5, 1, 2, 4, and 6 hrs post dose #7	48 hrs post Dose #1 (prior to Dose #7)
Day 4	8	NOTE: Serial PK can be done at Dose 7, 8, or 9 (based on site/patient convenience).	One sample anytime Day 4
	9		
	10		
Day 5	11		One sample anytime Day 5
	12		
	13		
Day 6	14		
	15		
			8-24 hrs post Dose #15
Day 7			Any time
Day 8			Any time
Day 14			Any time
Day 28			Any time

**Table 3-5 BID dosing beginning before 4 PM, with 2 doses given on Day 1:  
 Timing of samples for PK, viral load, and NS1**

For BID Dosing (with 2 doses given on Day 1)			
Day	Dose #	PK draw	Viral load and NS1
Day 1	1	Predose	Predose
	2		
Day 2	3	24 hrs post Dose #1 (prior to Dose #3)	24 hrs post Dose #1 (prior to Dose #3)
	4		
Day 3	5	Predose #5 AND 0.5, 1, 2, 4, 6, and 8 hrs post dose #5 NOTE: Serial PK can be done at Dose 5, 6 or 7 (based on site/patient convenience.)	48 hrs post Dose #1 (prior to Dose #5)
	6		
Day 4	7		One sample anytime Day 4
	8		
Day 5	9		One sample anytime Day 5
	10		
Day 6			8-24 hrs post Dose #10
7			Any time
8			Any time
14			Any time
28			Any time

**Table 3-6 BID dosing beginning between 6 PM and 10 PM, with 1 dose given on Day 1: Timing of samples for PK, viral load, and NS1**

For BID Dosing (with 1 doses given on Day 1)			
Day	Dose #	PK draw	Viral load and NS1
Day 1	1	Predose	Predose
Day 2	2		
	3	24 hrs post Dose #1 (prior to Dose #3)	24 hrs post Dose #1 (prior to Dose #3)
Day 3	4		
	5	Predose #5 AND 0.5, 1, 2, 4, 6 and 8 hrs post dose #5	48 hrs post Dose #1 (prior to Dose #5)
Day 4	6	NOTE: Serial PK can be done at Dose 5, 6 or 7 (based on site/patient convenience.	One sample anytime Day 4
	7		
Day 5	8		One sample anytime Day 5
	9		
Day 6	10		8-24 hrs post Dose #10
Day 7			Any time
Day 8			Any time
Day 14			Any time
Day 28			Any time

#### 4. STUDY POPULATION

Approximately 60 subjects will be enrolled in the study at approximately 40 study sites. Subjects will be adults with confirmed DENV infection.

##### 4.1 INCLUSION CRITERIA

A patient must meet the following criteria to be eligible for participation in this study:

1. 18-55 years of age at time of screening
2. Fever  $\geq 38^{\circ}\text{C}$  (or feeling feverish) with onset during the previous 60 hours
3. Positive test confirming DENV on a NS1 antigen test or RT-PCR assay
4. Negative rapid diagnostic test results for SARS-CoV-2 and Influenza A and B
5. Body mass index (BMI) of 18 to 30  $\text{kg/m}^2$

6. Provides written informed consent prior to initiation of any study procedures
7. Able to understand and agrees to comply with planned study procedures and be available for all study visits
8. Males and females of childbearing potential must agree to use protocol-specified methods of contraception as described in [Section 4.1.1](#)
9. Male subjects must agree to not donate sperm from the first dose through 90 days after the last dose of study drug

#### **4.1.1 Protocol Specified Methods of Contraception**

- Female subjects of childbearing potential must agree to use one of the following methods of birth control from screening through 30 days after the last dose of study drug:
  - intrauterine device (IUD)
  - bilateral tubal occlusion
  - vasectomized partner
  - sexual abstinence
  - hormonal contraception (including combined, progesterone only or intrauterine hormone-releasing system [IUS]) together with a barrier method such as (i) male or female condom with or without spermicide or (ii) cap, diaphragm or sponge with spermicide

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

- Male subjects must agree to use a condom from the first dose through 90 days after the last dose of the study drugs. If their female partner is of childbearing potential, the male subject must agree to discuss with his female partner the importance of using one of the additional contraceptive methods listed above from the first dose through 90 days after the last dose of study drug.
- Male subjects must have agreed not to donate sperm from the first dose through 90 days after the last dose of study drug.

#### **4.2 EXCLUSION CRITERIA**

A patient who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant at screening or plans to become pregnant within 90 days of screening
2. Female patient who is breastfeeding or plans to breastfeed during the study period
3. Has previously received any investigational or approved vaccine for dengue
4. Previous history of HIV, active chronic hepatitis B infection, or current hepatitis C infection (from medical history)
5. Use of any antiviral drug within 30 days or within 5 half-lives (whichever is longer) of the active drug or metabolite (for long-acting antivirals) of screening
6. Currently enrolled in or plans to participate in another clinical trial with an investigational agent or device that will be received during the study-reporting period
7. Exposure to another investigational agent within 30 days or 5 half-lives, whichever is longer, prior to study drug administration
8. Concomitant use of herbal or natural supplements or grapefruit juice (e.g. St. John's Wort, echinacea, milk thistle) or grapefruit juice. These should be discontinued at screening if the investigator feels that they can be safely discontinued or substituted for the duration of the study.
9. Patients with chronic medical conditions that put them at risk for severe dengue, including uncontrolled diabetes mellitus, severe asthma requiring oral steroids, and admission to the hospital in the previous 6 months for cardiac disease
10. Current use of anticoagulant or antiplatelet drugs or documented medical history of bleeding disorders
11. Malabsorption syndrome or other conditions that would interfere with enteral absorption
12. Immunocompromised due to use of immunosuppressive drugs including systemic corticosteroids (inhaled or topical corticosteroids are allowed) or any current disease or immunocompromised due to any current disease or condition
13. Use of P-glycoprotein (P-gp) inducers and inhibitors as described in [Section 5.6.1](#). *Note: hydroxychloroquine and amiodarone are prohibited within 3 months prior to screening and during the study.*

14. Evidence of severe dengue disease including:

- Severe plasma leakage leading to shock or fluid accumulation with respiratory distress
- Severe bleeding (including any subjects with hemoglobin levels <13.0g/dL in males and <11.0g/dL in females)
- Severe organ impairment (e.g., elevated transaminases  $\geq 1,000$  IU/L, impaired consciousness, renal failure [including any subjects with creatinine clearance < 60 mL/min {Cockcroft Gault formula}, or heart impairment] [including any subjects with clinically significant abnormal ECG at Screening])

15. Suspected or confirmed acute illness thought to be caused by a pathogen other than DENV

16. Confirmed or suspected SARS-CoV-2 infection or contact with patients with confirmed SARS-CoV2 infection within 7 days prior to screening

17. ALT or AST > 5x upper limit of normal (ULN) or total bilirubin > 1.5x ULN (Gilbert's syndrome is exempt) or platelet count <80,000/mm<sup>3</sup> at the time of screening

18. Has any other medical disease or condition that in the opinion of the site principal investigator or appropriate sub-investigator, precludes study participation. This includes any acute, subacute, intermittent, or chronic disease or condition that would place the patient at an unacceptable risk of injury, render the patient unable to meet the requirements of the protocol, or interfere with the evaluation of responses or the patient's successful completion of the trial

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

### **4.3 WITHDRAWAL OF SUBJECTS FROM THE STUDY**

#### **4.3.1 Reasons for Withdrawal**

Subjects can withdraw consent and discontinue from the study or from treatment at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study or from treatment if the subject:

1. Is noncompliant with the protocol requirements;
2. Experiences an SAE or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study;
3. Becomes pregnant;
4. Is required to take a medication prohibited by the protocol; or
5. Requests an early discontinuation for any reason.

The investigator can also withdraw a subject upon the request of the sponsor, or if the sponsor terminates the study. Upon occurrence of an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

#### **4.3.2 Handling of Withdrawals**

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, any subject who withdraws from the study prematurely will undergo all EOS assessments. Any subject who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

All subjects who prematurely discontinue study treatment should be encouraged to remain in the study and maintain the same protocol schedule and assessments as described in [Table 3-1](#). This will allow for continued subject follow-up for key outcome data.

### **4.3.3 Replacements**

In the event there is at least one subject who withdraws without post-baseline virology data, with the exception of those who withdraw for safety or tolerability, enrollment may remain open or extended at each dose level/cohort to enroll additional randomization block(s) of 4 patients (3:1) to increase the likelihood that at least 15 active and 5 placebo subjects with evaluable virology data are included in each cohort. Any additional patients will be randomized through the same centralized randomization process.

## **5. STUDY TREATMENTS**

### **5.1 TREATMENTS ADMINISTERED**

All subjects will receive the study treatments as described in [Section 3](#). The time of the initial study drug administration will be called “0” hours. The study drug will be administered with approximately 240 mL of water. Up to an additional 240 mL of water will be allowed, if necessary, to aid in swallowing of the study drugs. Subjects will not engage in strenuous activity at any time during the treatment period. When morning blood draws are required, study drug will be administered after blood sample collection. Study drug may be taken with or without food. The timing of TID dosing is provided in [Section 3.1.2](#) and the timing of BID dosing is provided in [Section 3.1.3](#). Doses of AT-752 and matching placebo should be separated by 8 hours ( $\pm 2$  hours) for TID dosing and by 12 hours ( $\pm 2$  hours) for BID dosing. After Day 1, if a dose is delayed, it should be taken as soon as possible, but must be taken at least 6 hours before the next scheduled dose. Otherwise, the dose must be skipped and the next dose taken as scheduled. Study drug dose modifications are not permitted in the study.

Dosing will be stopped at the end of the 15-dose (TID) or 10-dose (BID) treatment period. At the end of treatment period, tablets corresponding to any missed doses should be returned to the site.

Subjects must take the dose that was assigned at randomization, unless they discontinue for one of the reasons noted in [Section 4.3.1](#).



### 5.1.1 Safety Review Committee

This study is designed such that moving to the next dosing cohort is allowed only after an unblinded safety data review of the previous cohort by the SRC.

Unblinded safety summaries (e.g., AEs, clinical laboratory test results, vital sign measurements, and 12-lead ECG results) will be reviewed by the SRC to evaluate safety and tolerability of a given dose.

Initiation of additional cohorts will occur based on an initial safety review by the SRC of available safety data (through Day 5) and available PK data of the prior cohort.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 5.2 INVESTIGATIONAL PRODUCTS

The study drugs that will be used are as follows:

Product	Supplied Formulation
AT-752 tablet	250 mg of AT-281, free base of the drug substance AT-752
Matching placebo tablet	0 mg of AT-281, free base of the drug substance AT-752

Further information on the study drug can be found in the investigator’s brochure ([Atea Pharmaceuticals](#)).

### 5.2.1 Study Drug Packaging and Storage

Atea Pharmaceuticals, Inc. will provide the investigator and clinical unit with adequate quantities of AT-752 and matching placebo. Detailed instructions for the preparation of study treatments will be provided separately to the pharmacy.

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions.

The storage condition for AT-752 and placebo is: 15 - 25°C.

### 5.2.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. Accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

## 5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

CCI will generate the randomization schedule. Eligible subjects will be enrolled into the current dose cohort at a ratio of 3:1 (active:placebo). Each subject will be randomly assigned to a treatment assignment through a centralized randomization process and will receive a unique randomization number linked to the blinded treatment assignment. Randomization will be stratified by geographic region.

CCI [REDACTED]  
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CCI [REDACTED]  
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[REDACTED]  
[REDACTED]

## 5.4 BLINDING

### 5.4.1 Blinding Procedures

This study will employ a double-blind study design. The study drug and matching placebo tablets will be identical in appearance.

As this is an early phase study, the Sponsor may perform unblinded interim reviews of the data during the course of the study. An interim snapshot of the study database may be taken after completion of the clinical conduct of each cohort from the corresponding treatment arm.

### 5.4.2 Breaking the Blind

CCI [REDACTED] will be responsible for maintaining the blind throughout the study. If a subject becomes seriously ill or pregnant during the study, the blind will be broken (via IRT) only if knowledge of the administered study drug will affect that subject's available treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact CCI [REDACTED] to explain the need for unblinding. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

## 5.5 TREATMENT COMPLIANCE

Treatment adherence will be assessed by a study medication log (patient diary), which will be completed by the clinic staff for in clinic doses and by the participant or mobile nursing staff for out of clinic doses.

The date and time of study drug administration will be recorded on the appropriate page of the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

CCI



CCI



## 5.6 PRIOR AND CONCOMITANT MEDICATIONS

Information regarding prior medications taken by the subject within the 30 days before signing the informed consent form (ICF) as well as concomitant medications taken after starting study drug will be recorded in the subject's eCRF. Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. This includes standard-of-care treatments/therapies for dengue should subjects deteriorate on-study due to their dengue infection. If a prohibited

concomitant medication is taken, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject from the study based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

### 5.6.1 Prohibited Therapy

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

- Any previously received investigational or approved vaccine for dengue
- Any antiviral drug within 30 days or within 5 half-lives (whichever is longer) of the active drug or metabolite (for long-acting antivirals)
- Exposure to another investigational agent within 30 days or 5 half-lives, whichever is longer, prior to study drug administration
- Concomitant use of herbal or natural supplements or grapefruit juice (e.g. St. John's Wort, echinacea, milk thistle). A washout period of at least 7 days must be observed prior to study drug dosing, if the investigator feels that they can be safely discontinued or substituted for the duration of the study
- Use of anticoagulant or antiplatelet drugs
- Use of medications for treatment of inflammatory bowel disease
- Use of immunosuppressive drugs including systemic corticosteroids (defined as prednisone equivalent of > 10 mg/day for > 2 weeks; inhaled or topical corticosteroids are allowed)
- Use of P-glycoprotein (P-gp) inducers and inhibitors as described below.
  - Note: hydroxychloroquine and amiodarone are prohibited within 3 months prior to screening and during the study.

CCI

P-gp inhibitors should be safely discontinued or substituted approximately 12 hours prior to the first dose of AT-752. Patients may resume use of the discontinued or substituted P-gp inhibitor approximately 12 hours after the final dose of AT-527. If the P-gp inhibitors cannot be safely discontinued or substituted, the subject must not be enrolled.

Note: Hydroxychloroquine and amiodarone are prohibited within 3 months prior to screening and during the study.

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

The following P-gp inducers are prohibited:

- Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine
- Rifamycins: rifabutin, rifampin, rifapentine
- St. John's Wort

CCI

## 5.6.2 Cautionary Therapy

CCI Based on the anticipated plasma concentrations of AT-281 and their transient nature, no clinically relevant drug-drug interaction (DDI) is anticipated.

### CYP3A4 based interaction

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>.

The investigator or designee should consider substituting or stopping CYP3A4 substrates with NTI during study treatment and resuming them approximately 12 hours after the final dose of AT-752. In the event that the CYP3A4 substrate with NTI cannot be safely discontinued or substituted, the patient must not be enrolled.

### Medical procedures

There are no specific medical procedures anticipated to impact evaluation of efficacy, safety or PK provided that the medical procedures 1) do not significantly alter the function of major organs involved in drug absorption, distribution, metabolism or elimination such as GI, liver

and kidneys; and 2) do not involve concomitant use of prohibited medications discussed above that may interfere with the PK AT-752.

## 6. STUDY ENDPOINTS

### 6.1 PRIMARY ENDPOINT

- Change in DENV viral load (DENV RNA as measured by RT-qPCR) from baseline

### 6.2 SECONDARY ENDPOINTS: PHARMACOKINETIC ENDPOINTS

- Plasma concentrations of AT-281 (and metabolites AT-551, AT-229, AT-219, and AT-273) for each cohort at the following timepoints:
  - Day 1: Pre-dose (before the first dose, time 0)
  - 24 hours after Dose 1 (before Dose 4 for TID dosing and before Dose 3 for BID dosing)
  - A day of intensive PK sampling:
    - i. For TID dosing, samples will be obtained before Dose 7 and 0.5, 1, 2, 4, and 6 hours after Dose 7. This serial PK sampling may be done for Dose 7, 8, or 9, based on site/patient convenience
    - ii. For BID dosing, samples will be obtained before Dose 5 and 0.5, 1, 2, 4, 6, and 8 hours after Dose 5. This serial PK sampling may be done for Dose 5, 6, or 7, based on site/patient convenience

For blood samples (both TID and BID dosing), a  $\pm 10$ -minute window for time points  $\leq 4$  hours;  $\pm 15$  minute for time points between 4 and 24 hours

  - At any early study discontinuation visits. The timing of these PK samples relative to the last 2 (most recent) doses will be recorded
- Noncompartmental analysis will be performed for the following plasma PK parameters, when applicable and if data permit. Other PK parameters may also be calculated. PK parameters, where applicable, will be calculated based on actual times:
  - $AUC_{last}$  (area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration)
  - $AUC_{tau}$  (area under the plasma concentration versus time curve over the dosing interval)

- $AUC_{inf}$  (area under the plasma concentration versus time curve from time 0 to extrapolated to infinity)
- $C_{max}$
- $T_{max}$
- $t_{1/2z}$  (apparent terminal elimination half-life)
- CL/F for AT-281 only (apparent oral clearance)
- $V_z/F$  for AT-281 only (apparent volume of distribution)
- $C_{trough}$

### **6.3 SECONDARY ENDPOINTS: SAFETY ENDPOINTS**

- Incidence and grade of any TEAEs from first dose through Day 28 or withdrawal from the study
- Incidence and grade of any SAEs through Day 28 or withdrawal from the study
- Vital sign measurements
- Physical examination findings
- Clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis findings)
- ECG findings

### **6.4 EXPLORATORY ENDPOINTS: PHARMACODYNAMIC ENDPOINTS**

- Change in DENV viral load (as measured by infectious viral titre) from baseline
- Area under the log<sub>10</sub>-transformed viral load curve (AUC) from first dose to the end of treatment or study (as measured by DENV RNA and viral titre)
- Time to viral load clearance, which is defined as the first of 2 consecutive undetectable viral load measurements (as measured by DENV RNA and viral titre)



- Time to clearance of NS1 protein using NS1 antigen test. Clearance is defined as time from start of treatment until the first of 2 consecutive plasma samples are NS1-negative.
- Change of DENV viral load (as measured by DENV RNA and viral titre) from baseline, viral load AUC, time to viral load or NS1 clearance by DENV serotype
- Treatment-emergent amino acid substitutions in DENV NS5 polymerase
- Time to resolution or duration of fever Exploratory biomarkers on immunological response to dengue (See list in [Section 8.3.4](#))
- Exploratory analyses may be performed to evaluate exposure-response relationship. The relationship between the exposure of AT-752 (and its metabolites) and DENV viral load may be explored using graphical displays

## 7. STUDY ASSESSMENTS

Before performing any study procedures, all potential subjects will sign an ICF as outlined in [Section 10.2.2.3](#). Subjects will undergo study procedures at the time points specified in the SOE ([Section 3](#)). The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

### 7.1 PHARMACOKINETIC ASSESSMENTS

PK plasma samples will be collected as described in [Section 6.2](#). For blood samples, there is a  $\pm 10$  minutes window for time points  $\leq 4$  hour and a  $\pm 15$  minutes window for time points between 4 and 24 hours.

Pharmacokinetic endpoints will be characterized as subject numbers and PK data permit.

#### 7.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical sites in the study manual.

#### 7.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assays for AT-752 and metabolites AT-551, AT-229, AT-219

and AT-273 in human plasma. Assay results and validation details will be provided in a separate bioanalytical report.

## **7.2 PHARMACODYNAMIC ASSESSMENTS**

Temperature readings will be performed at least 4 times daily through the end of treatment (morning, mid-day, late afternoon, and evening; approximately every 4 hours during waking hours). Temperature will be measured orally and recorded in a patient diary (and given to the site coordinator for entry in the eCRF).

A rapid point of care (POC) test for DENV NS1 antigen and a DENV serotype test will be performed at screening. Viral load will be assessed by measuring plasma viremia by viral titre and with a serotype-specific, real-time reverse transcription PCR assay at screening and on Days 1-8, Day 14, and Day 28. DENV NS1 will be measured by ELISA at screening and on Days 1-8, Day 14, and Day 28. See [Section 3.1.4](#) for a description of the timing for collection of these samples.

## **7.3 SAFETY ASSESSMENTS**

Safety will be assessed by monitoring and recording of AEs, vital sign measurements, 12-lead ECG results, physical examination findings, and clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis).

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE reported on the AE page of the subject's eCRF. The investigator will monitor the subject until the result has reached the reference range or the result at screening, or until the investigator determines that follow-up is no longer medically necessary.

### **7.3.1 Adverse Events**

Adverse events will be assessed from the time of screening until EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical

significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

### 7.3.1.1 **Adverse Event Definitions**

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a study drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the study drug caused the event.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or if it occurs with specificity or severity that has not been previously observed with the study drug being tested; or, if an investigator brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

An AE or suspected adverse reaction is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered “life threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that might have caused death if it had been more severe.

### 7.3.1.2 **Eliciting and Documenting Adverse Events**

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and --over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

### 7.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. The Medical Dictionary of Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or which meets SAE criteria ([Section 7.3.1.1](#)) must be reported to the sponsor within 24 hours of awareness (after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE. The investigator is responsible for notifying the Institutional Review Board (IRB) or Ethics Committee (EC) directly as applicable per institutional policy. The sponsor or designee will provide regulatory authorities, IRB/ECs, and the investigator with clinical safety updates/reports according to local requirements

In addition to entering the AE details in the eCRF, the study site should also complete the SAE eCRF page within 24 hours of awareness. In the event that EDC entry is not possible (e.g., eCRF system failure or access problems), the study site should complete/fax the paper SAE report form and fax the form within 24 hours of awareness and update the EDC as soon as it is available.

For this study, the following contact information will be used for SAE reporting:

Email (primary):

PPD

<b>24 Hour Safety Hotline Fax:</b>
PPD

Back-up email: PPD

Fax (back-up): PPD

Phone (back-up): PPD

Additional follow-up information, if required or as available, should be sent as soon as possible and placed with the original SAE information.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a Pregnancy Notification Form. To ensure subject safety, each pregnancy must be reported to the sponsor within 2 weeks of learning of its occurrence. All pregnancies will be followed up to determine the outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications, even if the subject was discontinued from the study. After the expected pregnancy end date, the site will complete the Pregnancy Outcome Form. Elective terminations for medical reasons should not be reported as AEs or SAEs. Spontaneous miscarriages must be reported as an SAE. Any subject who becomes pregnant during the study must be withdrawn from the study

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#### 7.3.1.4 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities. Severity of AEs will be graded according to the grading scales modified from DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ([DHHS 2017](#)).

The determination of severity not listed in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2017) should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Grade 1 (Mild): Mild symptoms causing no or minimal interference with usual social and functional activities with no intervention indicated
- Grade 2 (Moderate): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
- Grade 3 (Severe): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated
- Grade 4 (Potentially life-threatening): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
- Grade 5 (Death)

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

#### 7.3.1.5 **Assessment of Causality**

The investigator's assessment of an AE's relationship to study drug is part of the documentation process.

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study drug. The AE does not follow a reasonable temporal sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
- Related: There is a reasonable possibility of relationship to study drug. The AE follows a reasonable temporal sequence from study drug administration and cannot be

reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications), represents a known reaction to the study drug or other drugs in its class, is consistent with the known pharmacological properties of the study drug, and/or resolves with discontinuation of the study drug (and/or recurs with re-challenge, if applicable).

### 7.3.1.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

### 7.3.2 Clinical Laboratory Testing

Clinical laboratory tests will be performed by the study sites' local laboratories. Blood and urine samples will be collected, as per the SOE (Section 3) and will be prepared using standard procedures.

A repeat measurement of clinical laboratory testing is permitted for eligibility determination. Other clinical laboratory retests may be permitted once in certain scenarios with CCI approval. Such scenarios may include laboratory processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting screening laboratory results. The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter.

The following clinical laboratory assessments will be performed at site or laboratory appointed by site:

Hematology	Complete blood count (CBC) including white blood cell (WBC) count with differential count, red blood cell (RBC) count, platelet count, hematocrit, hemoglobin, red blood cell indices
Coagulation	Prothrombin time, partial thromboplastin time, and international normalized ratio (INR)
Serum chemistry	Alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), bilirubin (total and direct), blood urea nitrogen (BUN), creatinine, lipase, serum creatine kinase, bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, total protein, albumin, phosphate, calcium, and amylase



Urinalysis	Urinalysis will be performed with microscopy at indicated. Additional urinalysis may be performed as clinically indicated. It is not required to have the results from the urinalysis performed at screening before beginning study drug dosing, unless medically necessary to establish eligibility (at investigator's discretion)
Direct viral tests	SARS-CoV-2 rapid test, rapid influenza diagnostic test
Other analyses	Female subjects: Pregnancy test ( $\beta$ -HCG; urine at screening and urine or serum after screening)

Samples for the following laboratory tests will be sent to the sponsor or a designee for analysis:

- Viral Load (as measured by RT-PCR and viral titre)
- Treatment-emergent amino acid substitutions in DENV NS5 polymerase
- DENV Serotype Testing
- NS1 Antigen
- Plasma Biomarker
- Pharmacokinetic Assessment

### 7.3.3 Vital Sign Measurements

Vital signs will be measured after the subject has been in the seated position for at least 5 minutes. A repeat measurement of vital sign measurements is permitted for eligibility determination. On Day 1, vital signs will be measured before study drug administration and before any scheduled blood collections ([Section 3](#)). Subsequent measurements of vital signs (once a day on Days 2-6) may occur anytime during the day, either in the clinic or with mobile nursing staff.

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

In addition, temperature will be measured orally at least every 4 hours during the study treatment period (morning, mid day, late afternoon, evening, while the subject is awake) and will be recorded in a patient diary.

### **7.3.4 12-Lead Safety Electrocardiogram**

Triplicate 12-lead ECG recordings will be performed as listed in the SOEs ([Section 3](#)) after the subject has been in the supine position for at least 5 minutes.

Measurements of the following intervals will be reported: RR interval, PR interval, QRS width, QT interval, and Fridericia's corrected QT interval (QTcF). Assessments should include comments on whether the tracings are normal or abnormal; rhythm; presence of arrhythmia or conduction defects; morphology; any evidence of myocardial infarction; or ST-segment, T Wave, and U Wave abnormalities.

### **7.3.5 Physical Examinations**

A complete physical examination will include, at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. A symptom-targeted physical examination will be conducted based on the specific symptoms targeted. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

## **8. STATISTICAL ANALYSIS**

Details of all statistical analyses will be described in a separate statistical analysis plan (SAP).

### **8.1 SAMPLE SIZE CALCULATIONS**

The sample size for this study is approximately 60 subjects. Each of the 3 cohorts will include 20 subjects (15 subjects receive AT-752 and 5 subjects receive placebo).

In Low et al ([Low 2014](#)), the observed standard deviations for VLR, defined as mean change from baseline viral load on days 2, 3, and 4, ranged from 0.75 (N=26) to 1.07 (N=24). Taking into account that the VLR endpoint in that study was based on an average of 3 measurements and assuming that there is some correlation between measurements on days 2 through 4, we consider power to detect a true effect at a single time point using a one-sided 0.10 level test (unadjusted for multiple comparisons) with N=15 per arm for standard deviations in a range from 1 to 1.75:

True standard deviation	Effect (log 10 copies/ml) with 80% power (N=15 vs. 15)  Comparison versus placebo pooled across 3 planned cohorts	Effect (log 10 copies/ml) with 80% power (N=15 vs. 5)  Comparison versus placebo within a cohort
1	0.8	1.1
1.25	1	1.4
1.5	1.2	1.7
1.75	1.4	2.0

Based on the above table, there is 80% power to detect a true treatment effect (versus placebo) on change-from-baseline viral load of 1 log<sub>10</sub> at a time point if the true SD is 1.25 for comparison of groups with N=15 each. The analogous power to detect a 1 log<sub>10</sub> effect for a within cohort comparison is 59%. Furthermore, if true SD is in the range from 1 to 1.75, the probability that the observed effect would be 0.5 log<sub>10</sub> or larger is low (in range from 0.09 to 0.22) if there is no treatment effect, i.e., an observed effect of 0.5 or larger might be considered suggestive of a signal. Interpretation of results will consider the totality of the data.

## 8.2 ANALYSIS SETS

The analysis populations are as follows:

- The primary analysis population is the modified intent-to-treat (mITT) population, which will include all randomized subjects who received at least 1 dose of study drug and have baseline and at least 1 post-baseline virology measurement. The primary analysis will also be performed on the per-protocol population of patients who completed treatment without a major protocol deviation.

- The PK population will include subjects who receive at least 1 dose of the study drug and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.
- The safety population will include all subjects who receive at least 1 dose of study drug.
- A per protocol population will include the subset of the modified intent-to-treat population who completed study drug treatment without a major protocol violation.

### **8.3 PLANNED STATISTICAL ANALYSIS**

Safety, PK, and PD data will be summarized in tabular and/or graphical format by active dose treatment arms and a-pooled placebo arm. Continuous data will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, 95% confidence interval [CI]) and categorical data will be summarized using counts and percentages. All subject-level data will be presented in listings.

Baseline demographic and background variables will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Incidence and percentage of subjects who withdraw or discontinue from the study and from treatment, and the reason for withdrawal or discontinuation, will also be summarized.

Baseline is the last measurement prior to the start of study drug.

#### **8.3.1 Primary Endpoint Analyses**

The primary objective of this study is to evaluate the antiviral activity of AT-752 compared with placebo on change from baseline in viral load (DENV RNA as measured by RT-PCR) based on the log-10 scale at specified timepoints.

Change from baseline in viral load will be compared between each AT-752 arm and the pooled placebo arm. Viral load will be analyzed using repeated-measures mixed model with treatment, time, and treatment-by-time interaction as fixed factors, with more details to be provided in the SAP. The treatment group least squares mean (LSM) estimates for mean change from baseline and treatment group differences at a time point, with 80% CI and p-value will be presented. Additionally, descriptive summaries for the change from baseline will also be presented by treatment group. Further details will be provided in the SAP.

### **8.3.2 Pharmacokinetic Analyses**

Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically.

Pharmacokinetic parameters derived from plasma samples using noncompartmental methods with Phoenix<sup>®</sup> WinNonlin<sup>®</sup> (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher or SAS Version 9.3 or higher (SAS Institute Inc., Cary, North Carolina) will be summarized by treatment and ethnicity using descriptive statistics (number of subjects, mean, SD, CV, geometric mean, geometric mean CV, median, minimum, and maximum). The parameter  $T_{max}$  will be summarized by treatment using the number of subjects, median, minimum, and maximum values.

### **8.3.3 Safety Analyses**

Adverse events will be coded by preferred term and system organ class using the latest version of the MedDRA. Severity of AEs will be graded according to the grading scales modified from DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2017). All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time. Where appropriate, graded laboratory abnormalities will be summarized by treatment (DHHS 2017). Shift tables will be generated to summarize baseline and post-baseline severity grades. Physical examination findings will be presented in a data listing.

### **8.3.4 Pharmacodynamic Exploratory Analyses**

- Change in DENV viral load (as measured by viral titre) from baseline
- Area under the log<sub>10</sub>-transformed viral load curve (AUC) from first dose to the end of treatment (Day 5-6) and to study end (Day 28) (as measured by DENV RNA and viral titre)

- Time to viral load (as measured by DENV RNA and viral titre) or NS1 clearance, defined as time to first of 2 consecutive undetectable viral load or NS1, will be described using Kaplan-Meier methods. The median time to viral clearance and the estimated proportions of patients with viral clearance will be summarized by treatment group. Patients who do not receive a record a negative test result by RT-PCR/viral titre or NS1 antigen assay by the last observation timepoint will be treated as censored at the final scheduled evaluation time point.
- Change of DENV viral load (as measured by DENV RNA and viral titre) from baseline, viral load AUC, time to viral load or NS1 clearance by DENV serotype
- Treatment-emergent amino acid substitutions in DENV NS5 gene
- 
- Methods for analysis of time to resolution or duration of fever will be presented in the SAP
- Exploratory biomarkers may include plasma concentrations of cytokines (for example, TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-1 $\beta$ , IP-10 and MCP-1)
- Exploratory analyses may be performed to evaluate exposure-response relationship. The relationship between the exposure of AT-752 (and its metabolites) and DENV viral load may be explored using graphical displays

## 8.4 HANDLING OF MISSING DATA

In general, observed data will be used in statistical analysis without imputation, unless missing data will jeopardize the integrity of the study or pose a problem in the validity of the analysis. A data-as-observed (DAO) approach will be used to evaluate the primary endpoint. Uncertain viral load measurements that are below the lower limit of quantification (LLOQ) will be set to  $0.5 \times \text{LLOQ}$  in the viral load summaries and indicated as BLQ in the listings. Impact of missing data will be assessed, and sensitivity analysis will be performed when deemed appropriate. Details will be described in the SAP.

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## 10. APPENDICES

### 10.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
AUC	area under the plasma concentration versus time curve
AUC <sub>inf</sub>	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
AUC <sub>last</sub>	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
AUC <sub>tau</sub>	area under the plasma concentration versus time curve over the dosing interval
BID	twice a day
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL/F	apparent oral clearance
C <sub>max</sub>	maximum observed plasma concentration
CRO	Contract Research Organization
C <sub>trough</sub>	trough concentration
CV	coefficient of variation
DAA	direct-acting antiviral
DENV	dengue virus
DNA	deoxyribonucleic acid
DtP	direct to patient
EC	Ethics Committee
ECG	electrocardiogram
eConsent	electronic consent
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
FDA	Food and Drug Administration
GMR	geometric mean ratio
HCV	hepatitis C virus
HED	human equivalent dose
HHC	home health care
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonization
INR	international normalized ratio
IRB	Institutional Review Board

<b>Abbreviation</b>	<b>Term</b>
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LSM	least squares mean
MAD	multiple ascending doses
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
NS1	nonstructural protein 1
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POC	point of care
QD	once daily
QTc	QT interval corrected for heart rate
RBC	red blood cell
RdRp	RNA-dependent RNA polymerase
RIDT	rapid influenza diagnostic test
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation(s)
SOE	schedule of events
SRC	Study Review Committee
$t_{1/2, z}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TID	3 times a day
$T_{max}$	time to maximum observed plasma concentration
TP	triphosphate
ULN	upper limit of normal
$V_z/F$	apparent volume of distribution
WBC	white blood cell

## **10.2 APPENDIX 2: STUDY GOVERNANCE**

### **10.2.1 Data Quality Assurance**

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures.

Important protocol deviations ([Section 10.2.4](#)), should they occur during the study, will be presented in [Section 10.2](#) of the clinical study report.

### **10.2.2 Investigator Obligations**

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/EC but will not result in protocol amendments.

#### **10.2.2.1 Confidentiality**

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, or the IRB/EC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

#### **10.2.2.2 Institutional Review**

ICH guidelines require that approval be obtained from an IRB/EC before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding

this study that is to be provided to the subject or the subject's legal guardian must be approved by the IRB/EC. Documentation of all IRB/EC approvals and of the IRB/EC compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/EC approvals should be signed by the IRB/EC chairperson or designee and must identify the IRB/EC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

### **Ethical Conduct of the Study**

The Study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

#### **10.2.2.3 Subject Consent**

Written informed consent in compliance with IRB/EC requirements shall be obtained from each subject before he or she enters the study or before performing any nonroutine procedure that involves risk to the subject. Prior to a subject's participation in the trial, the written ICF should be signed and personally dated by the subject/legally acceptable representative and by the person conducting the informed consent discussions. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/EC submission. Once reviewed, the investigator will submit the ICF to the IRB/EC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be allowed to read the approved ICF, ask any questions they have, and have adequate time to consider the information provided. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. The investigator must maintain the original and signed ICF. A copy of the ICF will be provided to the subject/legal guardian.

#### 10.2.2.4 **Study Reporting Requirements**

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB/EC as appropriate.

#### 10.2.2.5 **Financial Disclosure and Obligations**

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required as per IRB/EC and prior to subject enrollment. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

#### 10.2.2.6 **Investigator Documentation**

Prior to beginning the study, the investigator will be asked to comply with this Protocol, ICH E6(R2) [Section 8.2](#) and all applicable regulatory requirements by providing essential documents. The investigator will also provide all required essential documents during trial conduct and at trial termination in accordance with ICH E6 Guidelines.

#### 10.2.2.7 **Study Conduct**

The investigator agrees to perform all aspects of this study in accordance with the ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

#### 10.2.2.8 **Case Report Forms and Source Documents**

Site personnel will maintain source documentation, enter subject data into the electronic case report form (eCRF) as accurately as possible, and will rapidly respond to any reported discrepancies.

eCRFs and electronic data capture will be utilized. Each person involved with the study will have an individual identification code and password that allows for record traceability. The system, and any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

#### 10.2.2.9 **Adherence to Protocol**

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

#### 10.2.2.10 **Reporting Adverse Events**

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to the IRB/EC as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

#### 10.2.2.11 **Investigator's Final Report**

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/EC with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

#### 10.2.2.12 **Records Retention**

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period; however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

### 10.2.2.13 **Publications**

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

## 10.2.3 **Study Management**

### 10.2.3.1 **Monitoring of the Study**

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

### 10.2.3.2 **Study Digital Options**

- HHC (home health care): Home visits are allowed at certain visits as well as under reasonable occasional circumstances where the participant is unable to attend a clinic visit during the treatment period (see SOE; [Section 3.1](#)). Home visits will be conducted by qualified medical professionals with the permission of the Investigator and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.
- Televisits can support the completion of symptom-directed physical exams performed by HHC medical professionals via study phone calls with participants

### 10.2.3.3 **Inspection of Records**

The investigator and sites involved in the study will permit study-related monitoring, audits, IRB and EC review, and regulatory inspections by providing direct access to investigation facilities including drug storage and direct access to all original and/or certified copies of medical records and all study records. In the event of a sponsor audit, or a regulatory inspection, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports related to this study received to the sponsor.

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### 10.2.4 **Management of Protocol Amendments and Deviations**

#### 10.2.4.1 **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 subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).



#### 10.2.4.2 **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.

#### 10.2.4.3 **Study Termination**

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

#### 10.2.4.4 **Final Report**

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.