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. 125 Summer Street Boston, MA 02110 USA
Sponsor Contact:	PPD Atea Pharmaceuticals, Inc. PPD
Version of Protocol:	Protocol version 1.0
Date of Protocol:	20 September 2021

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.

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

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
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21-Sep-21 | 13:13 EDT
Date

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Atea Pharmaceuticals, Inc.

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Signer Name: PPD
Signing Reason: I approve this document
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PPD
Atea Pharmaceuticals, Inc.

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.

Investigator's Signature Date

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: 25-30 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 types 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 has developed 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 active metabolite, AT-9010. A first-in-human study (Protocol AT-02A-001) is being conducted in approximately 64 healthy adults in Australia to investigate the safety and pharmacokinetics (PK) (with embedded food effect), of AT-752. Part A of this study, assessing single ascending doses (SAD) in 40 subjects, has been completed. Part B of this study, assessing multiple ascending doses (MAD) is ongoing.

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. AT-281, the free base of AT-752, is a nucleotide prodrug that requires multistep metabolic activation to the pharmacologically active entity

The safety objective of this study is:

- To evaluate safety of AT-752 versus placebo assessed by treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), physical exams, vital signs, clinical laboratory assessments (including serum chemistry, coagulation, and hematology), and electrocardiogram (ECG) results 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, 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.

Upon randomization, subjects will be confined to the clinic and will receive their first dose.

For TID dosing, subjects will receive doses in the morning, at mid-day, and in the evening. Doses will be separated by approximately 8 hours. Subjects will be discharged on Day 6 (after end of treatment) and asked to return on Day 7, Day 8, and Day 14 (± 1 day) with a final safety follow-up performed on Day 28 (± 3 days). For clinical sites that decide to use mobile nursing, subjects may be discharged from the clinic on Day 2 and some of the additional visits (Days 4-5, Days 7-8, and Day 14) may be performed at investigator discretion through mobile nursing. The Day 1, Day 2, Day 3, Day 6, and Day 28 visits must be conducted at the clinical site.

The dose level for Cohort 1 has been determined based on review of PK and safety data from Part A (SAD) of the Phase 1 healthy volunteer study (Protocol AT-02A-001) in addition to preliminary data from Part B (MAD) of the study. Specific doses for Cohort 2 and Cohort 3 will be determined by a Safety Review Committee (SRC) after a review of all prior cohorts. Subjects who are enrolled in cohorts that are receiving BID dosing will receive doses in the morning and the evening. In those cohorts, doses will be separated by approximately 12 hours.

- 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, randomized cohort, subjects will receive AT-752 and placebo at 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 PK data through at least 5 days in the current dose cohort will undergo a blinded review by the SRC.

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 ≥38°C (or feeling feverish) with onset during the previous 48 hours
3. Live/work in or recent travel to dengue endemic area
4. Positive test confirming DENV on a NS1 antigen test or reverse transcription-polymerase chain reaction (RT-PCR) assay
5. Negative rapid diagnostic test result for SARS-CoV-2 and Influenza A and B
6. Body mass index (BMI) of 18 to 30 kg/m^2
7. Provides written informed consent prior to initiation of any study procedures
8. Able to understand and agrees to comply with planned study procedures and be available for all study visits
9. Males and females of childbearing potential must agree to use protocol-specified methods of contraception as described in Section 4.1.1
10. 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, 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 of the active drug or metabolite (for long-acting antivirals)
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. Use of herbal or dietary supplements or grapefruit juice within 7 days of screening (eg, chamomile, raspberry, peppermint, lemon, ginger, hibiscus, echinacea, rooibos, sage, lemon balm, rose hip, or passionflower tea, turmeric, ginger, bitter gourd, mangosteen, *Blumea balsamifera*, banaba [*Lagerstroemia speciosa*], soursop, bignay [Wild cherry], or horseradish [*Moringa oleifera*], artichoke, lotus, and other herbal cough treatments or herbal headache relievers in case of fever or cough)
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. Current use of medications for treatment of inflammatory bowel disease or documented medical history of chronic gastrointestinal disease including inflammatory bowel disease
12. Immunocompromised due to use of immunosuppressive drugs including systemic corticosteroids (inhaled or topical corticosteroids are allowed) or any current disease or condition
13. Evidence of severe dengue disease including:
    - Severe plasma leakage leading to shock or fluid accumulation with respiratory distress
    - Severe bleeding
    - Severe organ impairment (eg, elevated transaminases ≥1,000 IU/L, impaired consciousness, or heart impairment)
14. Suspected or confirmed acute illness thought to be caused by a pathogen other than DENV
15. Confirmed or suspected SARS-CoV-2 infection or contact with patients with confirmed SARS-CoV2 infection within 7 days prior to screening
16. 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^3 at the time of screening
17. 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 48 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 if BID dosing and 15 doses if 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 (± 1 day) and 28 (± 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 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, 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 ±10 minute window for time points ≤4 hours; ±15 minute for time points between 4 and 12 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 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 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

Exploratory Endpoints: PD Endpoints

- Area under the log10-transformed viral load curve (AUC) from first dose to the end of treatment or study
- Time to viral RNA clearance, which is defined as the first of 2 consecutive undetectable DENV viral RNA measurements
- 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 from baseline, viral load AUC, time to viral RNA, or NS1 clearance by DENV serotype
- 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 RNA measurement may be explored using graphical displays

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:
Oral dose levels of AT-752 will be evaluated across 3 sequential dosing cohorts:

- 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 (log10 copies/mL) with 80% power
1	0.8
1.25	1
1.5	1.2
1.75	1.4

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 log10 at a time point if the true SD is 1.25. Furthermore, if true SD is in the range from 1 to 1.75, the probability that the observed effect would be 0.5 log10 or larger is low (in range from 0.09 to 0.22) if there is no treatment effect, ie, 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 evaluate the antiviral activity of AT-752 compared with placebo on change from baseline in viral load based on the log-10 scale at specified timepoints.

Change from baseline viral load will be compared between each AT-752 arm and a combined placebo group. 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.

Safety, PK, and PD data will be presented in statistical summaries in tabular and/or graphical format by active dose treatment arms and one-pooling placebo treatment arm. Continuous data will be summarized in descriptive statistics (n, mean, SD, median, 95% CI) and categorical data will be presented in counts and percentages. All subject-level data will be presented in listings. Dose proportionality in PK will be assessed by a power model, if data permit.

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 include subjects who received at least 1 dose of study drug and have baseline and at least 1 post-baseline virology measurement.

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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 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 for DENV. The only licensed vaccine (Dengvaxia®) 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 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.

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In the current study, the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of AT-752 will be assessed in adult patients with confirmed DENV infection to support dose selection for future studies.

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 study (Protocol AT-02A-001) is currently being conducted in approximately 64 healthy adults in Australia to investigate the safety and PK (with embedded food effect) of AT-752. This Phase 1 first-in human, randomized, double-blind, placebo-controlled study is evaluating the safety, tolerability, and PK of AT-752 in healthy subjects. The study consists of 2 sequential parts: SAD (single ascending dose; Part A) and MAD (multiple ascending doses; Part B). Part A (SAD) includes a food effect cohort and both Part A (SAD) and Part B (MAD) cohorts are evaluating the potential effect of AT-752 on the QTc interval.

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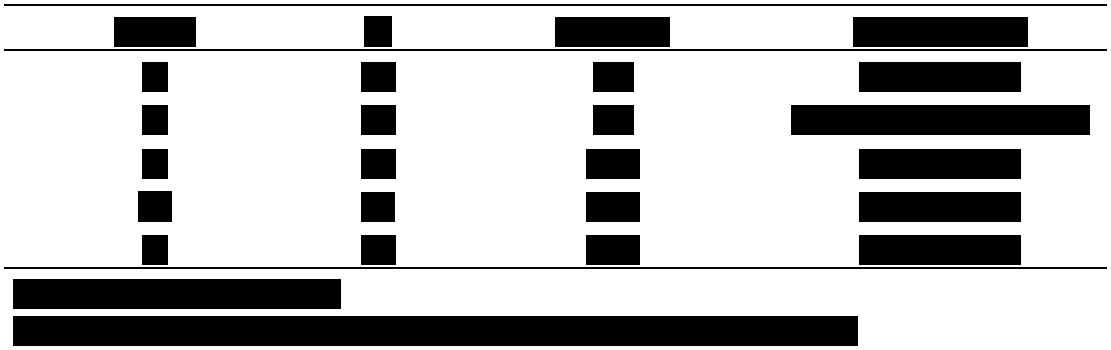

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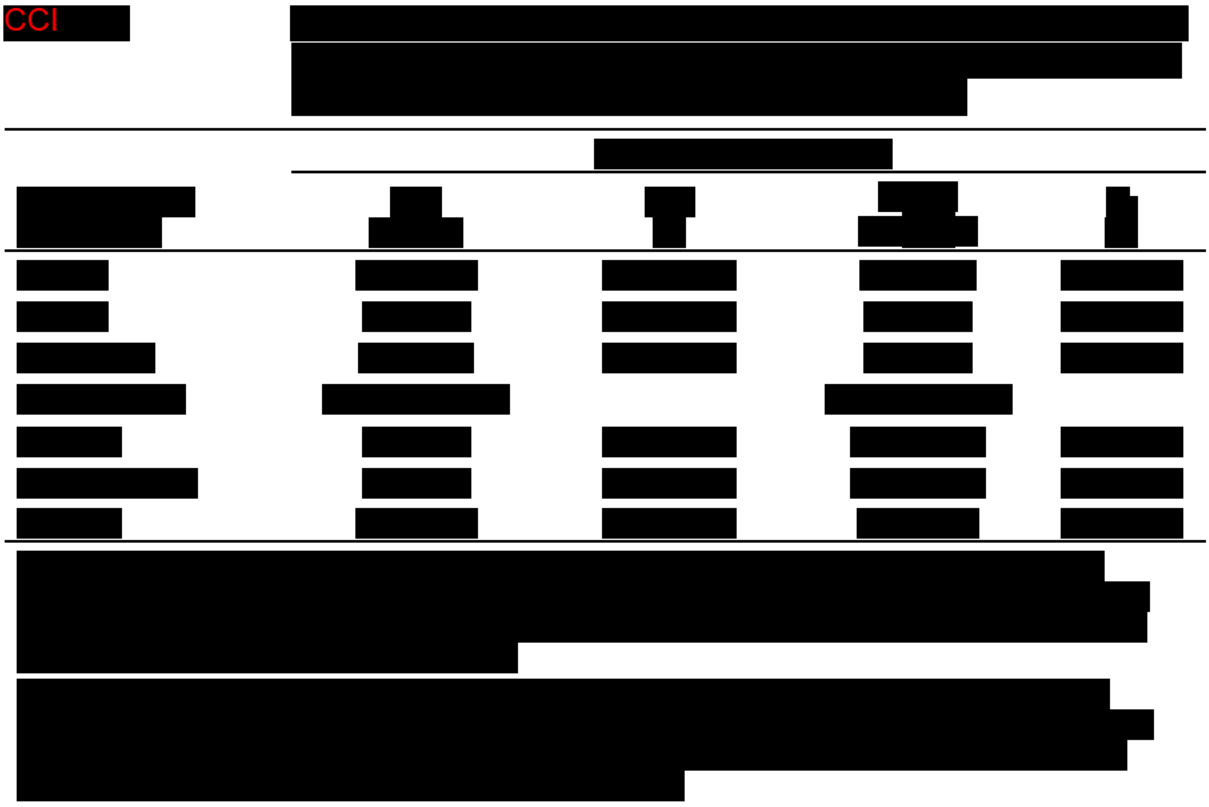

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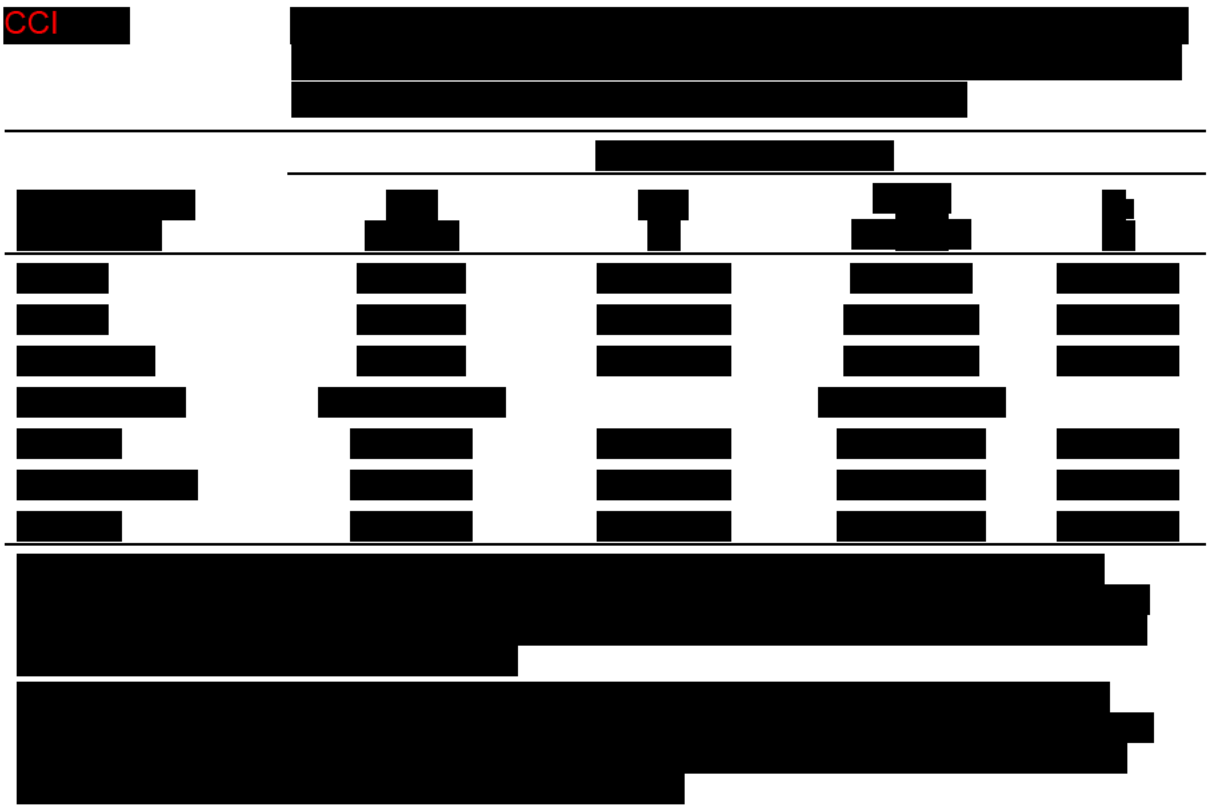

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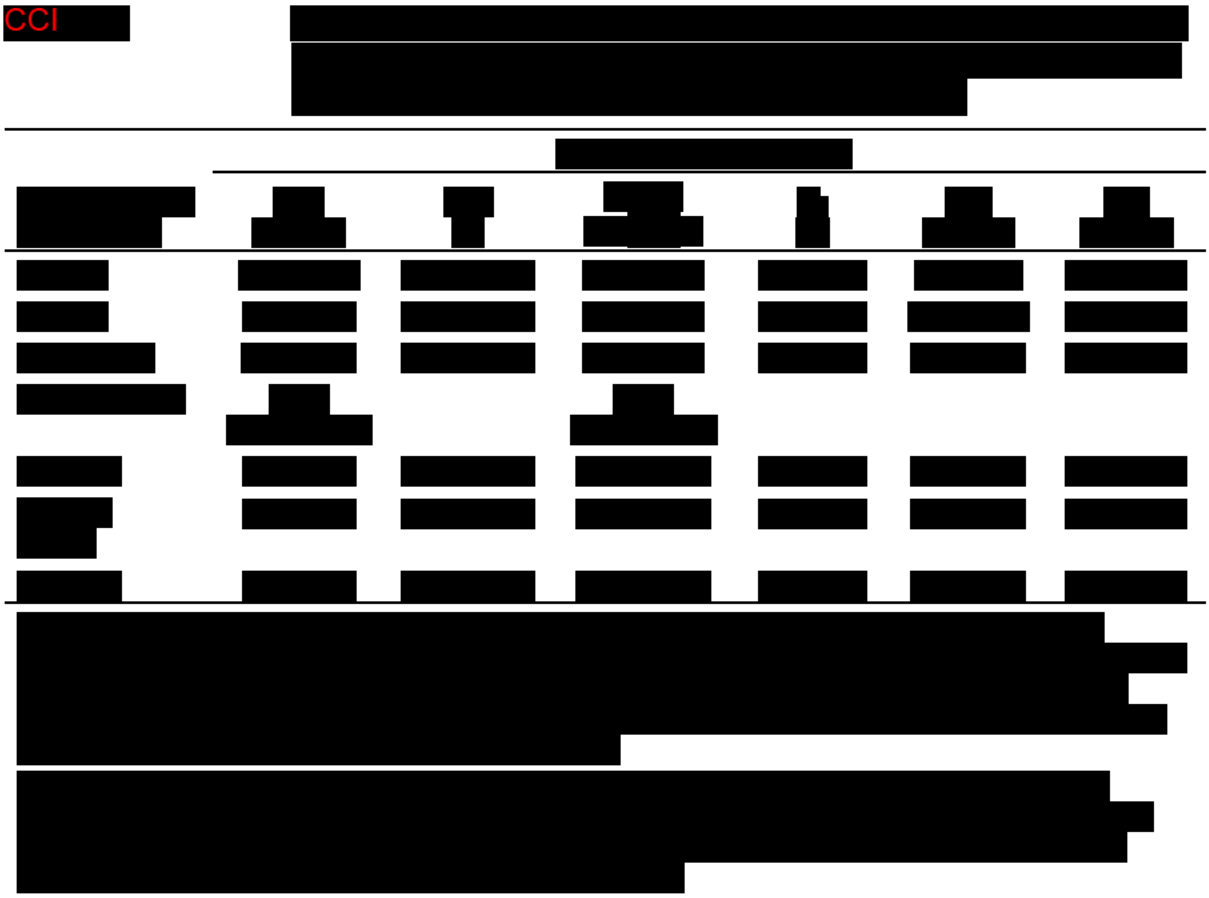

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1.3 RATIONALE FOR STUDY

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 has developed a novel purine nucleotide prodrug, AT-752, which is designed to treat patients that have been infected with the DENV. A first-in-human study is being conducted in approximately 64 healthy adults in Australia to investigate the safety and

PK (with embedded food effect), of AT-752. Part A of this study (Protocol AT-02A-001), assessing single ascending doses (SAD) in 40 subjects, has been completed. Part B of this study, assessing multiple ascending doses (MAD) is ongoing.

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

1.4 RATIONALE FOR DOSE SELECTION

Based on the rat and monkey no observed adverse effect level (NOAEL) of 1000 mg/kg/day of AT-752 (expressed as AT-281 free base) determined after 14 days of dosing, margins of safety have been calculated per FDA guidance for human doses of 1000 mg BID and 1000 mg TID (Table 1-7) (DHHS 2005). CCI [redacted]

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The dose level for Cohort 1 has been determined based on review of PK and safety data from Part A (SAD) of the Phase 1 healthy volunteer study (Protocol AT-02A-001) in addition to preliminary data from Part B (MAD) of the study. Specific doses for Cohort 2 and Cohort 3 will be determined by a Safety Review Committee (SRC) after a review of all prior cohorts. Based on the results of the AT-02A-001 study, 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

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. AT-281, the free base of AT-752, is a nucleotide prodrug that requires multistep metabolic activation to the pharmacologically active entity

The safety objective of this study is:

- To evaluate safety of AT-752 versus placebo assessed by TEAEs, serious adverse events (SAEs), physical exams, vital signs, clinical laboratory assessments (including serum chemistry, coagulation, hematology), and ECG results 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, 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 evaluating 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

*Study drug dosing:
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

Note: Initial study drug dosing should occur within 24 hours of screening and should occur on the same day as screening, when possible.

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 be confined to the clinic and will receive their first dose of study drug. Subjects in Cohort 1 will receive doses that are separated by approximately 8 hours (± 2 hours; morning, mid-day, and evening). Subjects will be discharged on Day 6 (after end of treatment) and asked to return on Day 7, Day 8, and Day 14 (± 1 day) with a final safety follow-up performed on Day 28 (± 3 days). For clinical sites that decide to use mobile nursing, subjects may be discharged from the clinic on Day 2 and some of the additional visits (Days 4-5, Days 7-8, and Day 14) may be performed at investigator discretion through mobile nursing. The Day 1, Day 2, Day 3, 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 initial dose level for Cohort 1 has been determined based on review of PK and safety data from Part A (SAD) of the Phase 1a healthy volunteer study (Protocol AT-02A-001). Specific doses for Cohort 2 and Cohort 3 will be determined by the SRC after a review of all prior cohorts. Subjects receiving BID dosing will receive doses that are separated by 12 hours (± 2 hours; morning and evening). 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, randomized cohort, subjects will receive active drug, and placebo at a 3:1 randomization. Each cohort will include 20 subjects (15 subjects receive AT-752 and 5 subjects receive placebo).

Prior to the initiation of each cohort after Cohort 1, all safety data through at least 5 days in the current dose cohort will undergo a blinded review by the SRC. Following each SRC review, the next cohort will be enrolled and proceed 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
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[a]	X								
Demographics	X								
Medical history	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Physical examination[b]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X				
12-lead ECG (triplicate-consecutive)	X				X				X
Chemistry/hematology/coagulation[d]	X	X	Day 2, 4		X		X	X	X
Urinalysis w/ microscopy[d]	X	X			X		X		
SARS-CoV-2 rapid test, RIDT[e]	X				X				
Pregnancy testing[f]	X								
NS1 rapid test[g]	X								
Pharmacokinetic assessments[h]		X	Day 2 and Day 3 or 4						
DENV serotype testing[i]	X								
Viral load[j]	X	X	X	X	X	X	X	X	X
NS1 antigen test	X	X	X	X	X	X	X	X	X
Adverse events[k]	X	X	X	X	X	X	X	X	X
Randomization	Prior to dosing								
Study drug administration		X	X	X					

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 creatinine kinase and lipase; 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 12 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 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. 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 should 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, the initial dose of study drug should be administered 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 possible, the initial dose of study drug should be administered on the same day as screening; if this is possible then the results of the vital signs obtained at screening will be used for the Day 1 vital sign results. Note that 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 consecutive12-lead ECG. If the initial dose of study drug is administered on the same day as screening, results of the screening ECG will be used for the Day 1 ECG results
- 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 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 viral load 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 (eg, at home) for subjects at sites that choose to use mobile nursing, except that the dose for PK evaluation (Dose 7, 8, or 9; see Section 3.1.4) must be taken under observation at the study site. 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 (± 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 (±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.

All other doses may be administered either at the study site or will be self-administered outside the study site (eg, 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 (± 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 (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 (± 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 (± 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 (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 (± 2 hours) timing of doses is adhered to.

Doses of study drug should be separated by 12 hours (±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.

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).

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 15). 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 (prior to Dose #4)	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		
	11		One sample anytime Day 4
	12		
Day 5	13		
	14		One sample anytime Day 5
	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		
	4	24 hrs post Dose #1 (prior to Dose #4)	24 hrs post Dose #1 (prior to Dose #4)
	5		
Day 3	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)
	8	NOTE: Serial PK can be done at Dose 7, 8, or 9 (based on site/patient convenience.	
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	48 hrs post Dose #1 (prior to Dose #5)
	6	NOTE: Serial PK can be done at Dose 5, 6 or 7 (based on site/patient convenience.	
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 25 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 enrollment
2. Fever ≥38°C (or feeling feverish) with onset during the previous 48 hours
3. Live/work in or recent travel to dengue endemic area
4. Positive test confirming DENV on a NS1 antigen test or RT-PCR assay
5. Negative rapid diagnostic test result for SARS-CoV-2 and Influenza A and B

6. Body mass index (BMI) of 18 to 30 kg/m^2
7. Provides written informed consent prior to initiation of any study procedures
8. Able to understand and agrees to comply with planned study procedures and be available for all study visits
9. Males and females of childbearing potential must agree to use protocol-specified methods of contraception as described in Section 4.1.1
10. 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 ≥ 54 years old with menses cessation for ≥ 12 months since previous menses, or a female of any age who had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation.
- 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, 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 of the active drug or metabolite (for long-acting antivirals)
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. Use of herbal or dietary supplements or grapefruit juice within 7 days of screening (eg, chamomile, raspberry, peppermint, lemon, ginger, hibiscus, echinacea, rooibos, sage, lemon balm, rose hip, or passionflower tea, turmeric, ginger, bitter gourd, mangosteen, *Blumea balsamifera*, banaba [*Lagerstroemia speciosa*], soursop, bignay [wild cherry], or horseradish [*Moringa oleifera*], artichoke, lotus, and other herbal cough treatments or herbal headache relievers in case of fever or cough)
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. Current use of medications for treatment of inflammatory bowel disease or documented medical history of chronic gastrointestinal disease including inflammatory bowel disease

12. Immunocompromised due to use of immunosuppressive drugs including systemic corticosteroids (inhaled or topical corticosteroids are allowed) or any current disease or condition

13. Evidence of severe dengue disease including:

    - Severe plasma leakage leading to shock or fluid accumulation with respiratory distress
    - Severe bleeding
    - Severe organ impairment (eg, elevated transaminases ≥1,000 IU/L, impaired consciousness, or heart impairment)
    - Suspected or confirmed acute illness thought to be caused by a pathogen other than DENV

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

15. 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^3 at the time of screening

16. 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 at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject is:

1. 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. Pregnant;
4. Required to take a medication prohibited by the protocol; or
5. Requesting 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.

4.3.3 Replacements

At the discretion of the investigator, subjects who have been randomized, but withdraw prior to dosing, may be automatically replaced. Additionally, after consultation with the medical monitor from the Contract Research Organization (CRO) for this study (CCI) and the sponsor, subjects who were dosed, but withdraw for reasons not related to safety of the study drug (eg, becoming infected with Covid) or who were lost to follow-up) before completing the study, may be replaced. Any replacement subject will be assigned to the same cohort and receive the same study drug as the subject being replaced.

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 (± 2 hours) for TID dosing and by 12 hours (±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.

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.

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.

5.1.1 Safety Review Committee

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

Study assessments (eg, AEs, clinical laboratory test results, vital sign measurements, and 12-lead ECG results) will be used 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 PK data of the prior cohort.

SRC charter will include safety related considerations.

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 2020).

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 cohort will be independently randomly assigned by a qualified person who is not directly involved in study conduct, data management, or data analysis. Randomization will be stratified by geographic region.

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. The unblinded pharmacist will be responsible for dispensing the study drug in a manner consistent with maintaining the blind.

As this is an early phase study, the Sponsor may perform unblinded interim reviews of the data during the course of the study. Interim study database locks may be performed after completion of the clinical conduct of each cohort and completion of the bioanalysis of samples 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 code break envelopes) 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 opening the code within 24 hours of opening the code. 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.

5.5.1 Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are provided in Sections 4.1 and 4.2. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

5.5.1.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the informed consent form (ICF) will be recorded in the subject's eCRF.

5.5.1.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject 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.

6. STUDY ENDPOINTS

6.1 PRIMARY ENDPOINT

- Change in DENV viral load from baseline

6.2 SECONDARY ENDPOINTS: PHARMACOKINETIC ENDPOINTS

- Plasma concentrations of AT-281 (and metabolites AT-551, AT-229, 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 ±10-minute window for time points ≤4 hours; ±15 minute for time points between 4 and 12 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 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

6.4 EXPLORATORY ENDPOINTS: PHARMACODYNAMIC ENDPOINTS

- Area under the log10-transformed viral load curve (AUC) from first dose to the end of treatment or study
- Time to viral RNA clearance, which is defined as the first of 2 consecutive undetectable DENV viral RNA measurements
- 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 from baseline, viral load AUC, time to viral RNA or NS1 clearance by DENV serotype
- 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 RNA measurement 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 9.2.2.3. 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 ±10 minute window for time points ≤4 hour and a ±15 minute window for time points between 4 and 12 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, 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 with a serotype-specific, real-time reverse transcription PCR assay at screening and on Days 1-8, Day 14, and Day 28. DENV NIS 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 (eg, 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 (eg, 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 6.3.1.1) 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 paper SAE report form and send the form to the contact information below, within 24 hours of awareness. In the event that EDC entry is not possible (eg, 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

24 Hour Safety Hotline:	24 Hour Safety Hotline Fax:
PPD	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 clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to the sponsor within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and

status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons should not be reported as AEs or SAEs. Spontaneous miscarriages must be reported as an SAE.

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 AIDS 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 intervention no 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 (ie, 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 (eg, 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 (eg, 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 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:

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 creatinine kinase
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)
Serology	DENV serotype testing (screening only)
Direct viral tests	SARS-CoV-2 rapid test, rapid influenza diagnostic test
Other analyses	Female subjects: Follicle-stimulating hormone, pregnancy test (β-HCG; urine at screening and urine or serum after screening)

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 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 include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen). 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.

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 (log10 copies/mL) with 80% power
1	0.8
1.25	1

1.5	1.2
1.75	1.4

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 log10 at a time point if the true standard deviation is 1.25. Furthermore, if true standard deviation is in the range from 1 to 1.75, the probability that the observed effect would be 0.5 log10 or larger is low (in range from 0.09 to 0.22) if there is no treatment effect, ie, 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 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.
- The PD population will include subjects who received at least 1 dose of study drug and have baseline and at least 1 post-baseline virology measurement.

8.3 PLANNED STATISTICAL ANALYSIS

Safety, PK, and PD data will be presented in statistical summaries in tabular and/or graphical format by active dose treatment arms and one-pooling placebo treatment arm. Continuous data will be summarized in descriptive statistics (n, mean, standard deviation [SD], median, 95% confidence interval [CI]) and categorical data will be presented in counts and percentages. All subject-level data will be presented in listings. Dose proportionality in PK will be assessed by a power model, if data permit.

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 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 based on the log-10 scale at specified timepoints.

Change from baseline viral load will be compared between each AT-752 arm and a combined placebo group. 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 a separate statistical analysis plan.

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® WinNonlin® (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, SpO_2, 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 Analyses

- Area under the log10-transformed viral load curve (AUC) from first dose to the end of treatment (Day 5-6) and to study end (Day 28)

- Time to viral RNA or NS1 clearance, defined as time to first of 2 consecutive undetectable viral RNA 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 or NS1 antigen assay by the last observation timepoint will be treated as censored at the final scheduled evaluation time point.

- 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-α, IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-1β, 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 RNA measurement may be explored using graphical displays

8.4 HANDLING OF MISSING DATA

Strategies for handling missing data will be described in the SAP.

9. REFERENCE LIST

Atea Pharmaceuticals, Inc. AT-752. Investigator's brochure, edition No. 1 Boston (MA). 2020.

Center for Disease Control and Prevention (CDC). Dengue. July 2020 [cited 03 Dec 2020] [13 screens]. Available from: https://www.cdc.gov/dengue/index.html.

Dengvaxia Package Insert. Jun 2019 [cited 03 Dec 2020] [16 pages] Available from: https://www.fda.gov/media/124379/download.

Department of Health and Human Services (DHHS), Food and Drug Administration (DHHS), Center for Drug Evaluation and Research (US). Guidance for industry: Food-effect bioavailability and fed bioequivalence studies. December 2002 [03 Dec 2020] [12 screens]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (US). Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 2005 [cited 03 Dec 2020] [30 screens]. Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf

Department of Health and Human Services (DHHS), National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. Version 2.1. July 2017 [cited 2020 Dec 10] [35 screens]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.

Low JG, Sung C, Wijaya L, et al. Efficacy and safety of celgosivir in patients with dengue fever (CELADEN): a phase 1b, randomised, double-blind, placebo-controlled, proof-of-concept trial. Lancet Infect Dis. 2014;14:706-715.

Low JG, Gatsinga R, Vasudevan SG, et al. Dengue Antiviral Development: A Continuing Journey. Adv Exp Med Biol. 2018;1062:319-32.

CCI [redacted]

Nguyen NM, Tran CN, Phung LK, et al. A randomized, double-blind placebo controlled trial of balapiravir, a polymerase inhibitor, in adult dengue patients. J Infect Dis. 2013;207(9):1442-50.

Rivera A, Adams LE, Sharp TM, et al. Travel-associated and locally acquired dengue cases-United States, 2010–2017. MMWR Morb Mortal Wkly Rep. 2020;69:149-154.

Thomas SJ and Yoon I-K. Hum A review of Dengvaxia®: development to deployment. Vaccin Immunother. 2019; 15(10): 2295–2314.Troost B and Smit JM. Recent advances in antiviral drug development towards dengue virus. Curr Opin Virol. 2020;43:9-21

Wilder-Smith A, Quam M, Sessions O, et al. The 2012 dengue outbreak in Madeira: exploring the origins. Euro Surveill. 2014; 19:20718.

World Health Organization (WHO). Dengue and severe dengue. June 2020 [cited 03 Dec 2020] [1 screen]. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.

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_{inf}	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
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
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_{max}	maximum observed plasma concentration
C-QTc	concentration-QTc
CRO	Contract Research Organization
C_{trough}	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 Harmonisation
INR	international normalized ratio

Abbreviation	Term
IRB	Institutional Review Board
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)
PBMC	peripheral blood mononuclear cell
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
Vz/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 9.2.3.2), 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/legal 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 time line 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

- eConsent (electronic consent): It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent
- 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 replace study phone calls with participants
- DtP (direct to patient): If allowed by country regulation/IRBs/ECs, study drug can be shipped DtP from the investigation site to the patient's home address via courier if needed.

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.

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 (eg, 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.