STATISTICAL ANALYSIS PLAN

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DATE OF PLAN:

15-NOV-2022

BASED ON:

Protocol Amendment 1, 29JUL2022

STUDY DRUG:

AT-752

PROTOCOL NUMBER:

AT-02A-002

STUDY 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

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS 5

1. INTRODUCTION 6

2. OBJECTIVES 6

2.1 PRIMARY OBJECTIVE 6
2.2 SECONDARY OBJECTIVES 6
2.3 EXPLORATORY OBJECTIVES 7

3. STUDY DESIGN 7

3.1 OVERALL STUDY DESIGN 7
3.2 STUDY ENDPOINTS 7
3.2.1 PRIMARY ENDPOINT 7
3.2.2 SECONDARY ENDPOINTS 7
3.2.3 EXPLORATORY ENDPOINTS 8

4. GENERAL STATISTICAL CONSIDERATIONS 9

4.1. SAMPLE SIZE 10
4.2. RANDOMIZATION, STRATIFICATION, AND BLINDING 11
4.3. ANALYSIS POPULATION 11

5. SUBJECT DISPOSITION 12

5.1 DISPOSITION 12
5.2 PROTOCOL DEVIATIONS 12
5.3 INCLUSION AND EXCLUSION CRITERIA 12

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS 13

6.1 DEMOGRAPHICS 13
6.2 MEDICAL HISTORY 13

7. TREATMENTS AND MEDICATIONS 13

7.1 PRIOR AND CONCOMITANT MEDICATIONS 13
7.2 MEDICAL OR SURGICAL TREATMENT PROCEDURES 13
7.3 STUDY TREATMENT 13

8. EFFICACY 14

8.1 PRIMARY EFFICACY 14
8.1.1 PRIMARY ENDPOINT 14
8.1.2 PRIMARY ENDPOINT SUPPORTIVE ANALYSES 14

9. SAFETY ANALYSIS 14

9.1 ADVERSE EVENTS 15
9.2 CLINICAL LABORATORY EVALUATIONS 16
9.3 VITAL SIGN MEASUREMENTS 22
9.4 PHYSICAL EXAMINATION 23
9.5 ELECTROCARDIOGRAMS 23

10. MISSING DATA HANDLING 23

11. PHARMACOKINETICS 24

11.1 DATA HANDLING 24
11.2 PLASMA PHARMACOKINETIC PARAMETERS 24

12. PHARMACODYNAMICS 25

13. INTERIM ANALYSIS 26

14. CHANGES IN THE PLANNED ANALYSIS 26

15. REFERENCES 26

List of Abbreviations

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
BLQ	Below the limit of quantification
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_{trough}	trough concentration
CSR	clinical study report
CV	coefficient of variation
DAA	direct-acting antiviral
DENV	dengue virus
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GMR	geometric mean ratio
ICH	International Council for Harmonization
LLOQ	Lower limit of quantification
LSM	Least Squares Mean
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NCA	noncompartmental analysis
NS1	nonstructural protein 1
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics

PK	pharmacokinetics
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SRC	Study Review Committee
$t_{1/2z}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{last}	time of last measurable observed concentration
TLF	table listing figure
T_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cell

1. Introduction

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods used to evaluate antiviral activity, safety, pharmacokinetics (PK), and pharmacodynamics (PD) data for Study AT-02A-002. This SAP is written based on AT-02A-002 protocol Amendment 1, dated on 29 July 2022.

Dengue fever is a mosquito-borne illness that is caused by 4 distinct serotypes of ribonucleic acid (RNA) viruses (DENV-1, DENV-2, DENV-3, and DENV-4) belonging to the flavivirus genus.

Atea Pharmaceuticals is developing a novel purine nucleotide prodrug, AT-752, which is designed to treat patients that have been infected with the dengue virus (DENV). When dissolved, AT-752 releases the freebase CCI , which in a series of steps is converted to the intracellular active triphosphate metabolite, AT-9010 (triphosphate of AT-273, and therefore plasma AT-273 is considered a surrogate of intracellular AT-9010). A first-in-human study (Protocol AT-02A-001) was completed in 65 healthy adults in Australia to investigate the safety and pharmacokinetics (PK) (with embedded food effect and PK ethnic sensitivity evaluation) of AT-752. 41 subjects received single ascending doses (SAD), and 24 subjects participated in the multiple ascending dose (MAD) portion of the study. The first-in-human study supported dose selection for the current study.

The Phase 2 study AT-02A-002 will be conducted in adult patients with confirmed DENV infection and will investigate antiviral activity, safety, PK, and PD in this population. This study will be conducted in several dosing cohorts to enable dose selection for subsequent trials.

2. Objectives

2.1 Primary Objective

- 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

2.2 Secondary Objectives

- To evaluate the safety of AT-752 versus placebo in adult subjects with confirmed DENV infection
- To evaluate the PK of AT-752 (CCI) and metabolites in adult subjects with confirmed DENV infection

2.3 Exploratory Objectives

- To describe the effect of AT-752 on viremia (viral titre), DENV nonstructural protein 1 (NS1) levels, fever, and biomarkers (see list in section 12) compared to placebo in adult subjects with confirmed DENV infection

3. Study Design

3.1 Overall Study Design

This study will enroll approximately 60 subjects in 3 cohorts who meet the inclusion/exclusion criteria. Following screening and informed consent, eligible subjects will be randomized (3:1) to receive either AT-752 or matching placebo either twice a day (BID) or 3 times a day (TID) for 5 days. The dose level for Cohort 1 has been determined on review of PK and safety data from the phase I healthy volunteer study (Protocol AT-02A-001). Specific doses for Cohort 2 and Cohort 3 will be endorsed by a Safety Review Committee (SRC) after an unblinded review of the previous 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

Each cohort will include 20 subjects (15 subjects receive AT-752 and 5 subjects receive placebo). Randomization will be stratified by geographic region. 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. Subjects will be discharged on Day 6 (after end of treatment) if hospitalized, and asked to return on Day 7, Day 8, and Day 14 (± 1 day) with a final safety follow-up performed on Day 28 (± 3 days). For clinical sites that decide to use mobile nursing, some of the subsequent visits (Days 24-5, Days 7-8, and Day 14) may be performed at investigator discretion through mobile nursing. The Day 1, Day 6, and Day 28 visits must be conducted at the clinical site. The maximum duration that any patient will be on study is 32 days.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary objective will be assessed by change in DENV viral load (DENV RNA as measured by RT-qPCR) from baseline.

3.2.2 Secondary Endpoints

Secondary endpoints corresponding to secondary objectives (Section 2.2) are:

Secondary objective	**Secondary endpoints**
Safety	• Incidence and grade of any treatment-emergent adverse events (TEAEs) from first dose through Day 28 or withdrawal from the study • Incidence and grade of any serious adverse events (SAEs) through Day 28 or withdrawal from the study • Vital sign measurements • Physical examination findings • Clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) findings • Electrocardiogram (ECG) findings
Plasma PK of AT-281 and metabolites	• Plasma concentrations of CCI-CCI and metabolites (AT-551, AT-229, AT-219, and AT-273) and derived PK parameters (AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{trough} (AT-273 only))

3.2.3 Exploratory Endpoints

Exploratory endpoints corresponding to exploratory objectives are:

Exploratory objective	**Exploratory endpoints**

PD	• Change in DENV viral load (as measured by infectious viral titre) from baseline • Area under the log 10-transformed viral load curve (AUC) from first dose to the end of treatment or study [as measured by DENV RNA and viral titre] • Time to viral load clearance, which is defined as the first of 2 consecutive undetectable viral load measurements [as measured by DENV RNA and viral titre] • Time to clearance of NS1 protein using a NS1 antigen test. Clearance is defined as time from start of treatment until the first of 2 consecutive plasma samples are NS1-negative. • Subgroup analysis by DENV serotype: Change of DENV viral load [as measured by DENV RNA and viral titre] from baseline, viral load AUC, time to viral load, or NS1 clearance by DENV serotype • Treatment-emergent amino acid substitutions in DENV NS5 polymerase • Time to resolution or duration of fever • Exploratory biomarkers on immunological response to dengue (See list in Section 12) • Exploratory analysis to evaluate exposure-response relationship. The relationship between the exposure of AT-752 (and its metabolites) and DENV viral load measurement may be explored using graphic displays.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Analysis of the data from this study will be descriptive in nature. Confidence intervals and p-values will be descriptive due to small sample size in this study. N, mean, standard deviation, median, minimum and maximum, and 95% CI will be used for continuous data and number and percentage

will be used for categorical/count data, unless specified otherwise. No analysis will be performed until the data are unblinded.

All tables, listings, and figures will be presented by assigned treatment. The treatments below will be used for presentations:

- AT-752 750 mg TID
- AT-752 up to 1000 mg BID or TID
- AT-752 up to 1500 mg BID
- Placebo (pooled Cohort 1 through Cohort 3)

All data listings will be sorted by treatment and subject number. If a regimen is repeated in more than one cohort, the matching cohorts will be pooled as one treatment.

Unless otherwise specified, no algorithm for imputation of missing data will be employed.

Study days are calculated with respect to the first date of study drug exposure (First Dose Date) as below:

- If the assessment/observation date is on or after the first dose date, then
  Study Day = Assessment/Observation Date – First Dose Date + 1;

- Otherwise, Study Day = Assessment/Observation Date – First Dose Date

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before administration of the first dose of study drug, unless otherwise specified.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining baseline, but will be presented in data listings.

The methodology and data handling specifications for PK data are detailed in Section 11.

4.1. Sample Size

The sample size for this study is up to 60 subjects and each cohort will include 20 subjects, allocated 3:1 (AT-752:placebo). 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 the study was based on an average of 3 measurements and assuming that there is some correlation between measurements on days 2 through

4, we consider power to detect a true effect at a single time point using a one-sided 0.10 level test (unadjusted for multiple comparisons) with N=15 per arm for SD in a range from 1 to 1.75:

True standard deviation	Effect (log 10 copies/ml) with 80% power (N=15 vs. 15)	Effect (log 10 copies/ml) with 80% power (N=15 vs. 5)
1	0.8	1.1
1.25	1	1.4
1.5	1.2	1.7
1.75	1.4	2.0

Based on the above table, there is 80% power to detect a true treatment effect (versus placebo) on change-from-baseline viral load of 1 log10 at a time point if the true SD is 1.25 for comparison of groups with N=15 each. The analogous power to detect a 1 log10 effect for a within cohort comparison is 59%. Furthermore, if true SD is in the range from 1 to 1.75, the probability that the observed effect would be 0.5 log10 or larger is low (in range from 0.09 to 0.22) if there is no treatment effect, i.e., an observed effect of 0.5 or larger might be considered suggestive of a signal. Interpretation of results will consider the totality of the data.

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

4.2. Randomization, Stratification, and Blinding

The randomization schedule will be generated prior to the initiation of the study. Subjects who meet all inclusion and none of the exclusion criteria will be randomly assigned in a 3:1 ratio to either experimental drug or placebo. Randomization will be stratified by geographic region. Randomization numbers (in sequential order) will be assigned before the first dose of study drug is administered on Day 1. This is a double-blind study: the investigator and the subject will be kept blinded to the treatment allocation.

4.3. Analysis Population

Primary endpoint analyses will be applied to the modified intent-to-treat population (mITT), which is defined as all randomized subjects who received at least 1 dose (full dose, unless assigned to placebo) of study drug (AT-752 or matching placebo) and have baseline and at least one post-baseline virology measurement. Change from baseline viral load (DENV RNA) will be compared between each AT-752 arm and a combined placebo group.

As-treated population is defined as all subjects who received at least 1 dose (full dose, unless assigned to placebo) of study drug (AT-752 or matching placebo) based on the actual treatment the patients received and had baseline and at least one post-baseline virology measurement.

The safety population will include all subjects who receive at least 1 dose of study drug.

The PK population will include all subjects who receive at least 1 dose of AT-752 and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. PK parameter summaries will include only subjects in the PK population who have sufficient concentration measurement data to support estimation of the parameter. All subjects excluded from the PK population will be documented in the data listings.

The PD population will be the mITT population, which includes subjects who received at least 1 dose (full dose, unless assigned to placebo) of study drug and have baseline and at least 1 post-baseline viral load measurement.

The Per Protocol (PP) population will include the subset of the modified intent-to-treat population who completed study drug treatment without a major protocol violation that impact patient safety or data quality.

5. Subject Disposition

5.1 Disposition

The following will be summarized for the full analysis set, by treatment and overall for all subjects:

- The number of subjects who completed the study drug per protocol
- The number of subjects who completed the study
- The number of subjects who did not complete the study and study drug treatment (both overall and according to reasons for discontinuation from the study and study drug treatment)
- The number of subjects in each analysis population.

Subject disposition data will be presented in a data listing.

5.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to Food and Drug Administration (FDA) regulations or International Council for Harmonization (ICH) E6(R2) guidelines. Important protocol deviations will be summarized by treatment for all randomized subjects. All protocol deviations will be presented in a data listing, including the categorization of the deviation as important or not.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a separate data listing.

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic information collected at screening will be presented in a data listing.

Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity

The summaries will be presented by treatment and overall for the safety population.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 24.1 or up) and presented in a data listing.

7. Treatments and Medications

7.1 Prior and Concomitant Medications

Medications that stop prior to the first dose of study drug will be classified as prior medication. Medications that start on or after the first dose of study drug will be classified as concomitant. If a

medication starts before the first dose of study drug and stops on or after the first dose of study drug, then the medication will be classified as both prior and concomitant.

All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (version to be delineated in the CSR) and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3 Study Treatment

Per the protocol, subjects are to receive study drug (AT-752 or matching placebo) orally either BID or TID for 5 days. Study treatment exposure (treatment duration and total dose received) will be summarized with descriptive statistics. A listing of patients, detailing dosing of study drug (including the timing of study drug administration) will be presented.

The duration of treatment exposure will be summarized with descriptive statistics for the safety population. The duration of treatment exposure [days] is defined as {(last dose date)-(first dose date)}+1. The total dose received will be summarized by the percentage of dose received relative to expected dose (per the protocol), where the unit for dose here will be the number of tablets. Study drug is administered as 250 mg tablets, so the expected number of tablets received is 45 tablets for 750 mg TID regimen, 40 tablets for the 1000 mg BID regimen, 60 tablets for the 1000 TID regimen, and 60 tablets for the 1500 mg BID regimen.

8. Efficacy

Primary efficacy endpoint analyses will be applied to the modified intent-to-treat population, which is defined as all randomized subjects who received at least 1 dose of study drug and have baseline and at least one post-baseline virology measurement. The primary analysis will also be performed on the per-protocol population of patients who completed treatment without a major protocol deviation.

8.1 Primary Efficacy

8.1.1 Primary Endpoint

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

$$y_i = v_i - v_0$$

where v_i is the log10 DENV viral load measured at timepoint t_i and v_0 is the log10 DENV viral load measured at baseline. Viral load measurements that are below the lower limit of quantification (LLOQ) will be set to 0.5 × LLOQ in the analysis.

Change from baseline in DENV viral load (y_i) will be analyzed with repeated measures mixed model using the method of restricted maximum likelihood (REML). The model will include baseline viral load, treatment, time, and treatment-by-time interaction as fixed factors. An unstructured covariance matrix will be specified for the repeated statement. In case a mixed model with unstructured (UN) covariance matrix fails to converge, a compound symmetry (CS) structure will be used as an alternative. If neither of these converges, independent (ID) structure will be used. If none of these converges, the change from baseline by scheduled time point (ANOVA, Kruskal-Wallis) analysis will be presented as the primary analysis. The treatment group least squares mean (LSM) estimates for mean change from baseline and treatment group differences at each time point, with 80% CI, 95% CI and p-value will be presented.

8.1.2 Primary Endpoint Supportive Analyses

The primary endpoint will also be analyzed using the same method in the as-treated population.

The following viremia descriptively summarized by treatment arm, with comparison method indicated in parentheses:

- Change from baseline in log10 viral load by scheduled time point (Kruskal-Wallis). Along with the Kruskal-Wallis test, a one-way ANOVA will be used to compare treatment effect separately at each time point.
- Proportion of measurements above the lower limit of quantification (Fisher exact)

All viremia data will be listed and individual profiles of viremia over time will be presented for each subject. Viremia levels below the lower limit of quantification will be considered as 0 in the log10 viral load summaries and indicated as BLQ in the listings.

9. Safety Analysis

All safety summaries and analyses will be based upon the safety population. Summaries will be presented by treatment group and overall.

9.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: not related, or related. If the relationship information is missing, the AE will be considered related in the summary but will be presented as missing in the data listings.

A treatment-emergent AE (TEAE) 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. The time frame for treatment emergent adverse events in this study is from the first dose through Day 28 or withdrawal from the study, whichever happens first. TEAE that are evaluated as possibly related to study drug, regardless of timing, will be considered treatment-related TEAE for summary purpose.

The severity of AEs will be classified by the investigator as Grade 1 mild, Grade 2 moderate, Grade 3 severe, Grade 4 potentially life threatening and Grade 5 death. If the severity information is missing, the AE will be considered severe in the summary but will be presented as missing in the data listings.

In all AE summaries, a subject with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of subjects in the safety population.

An overall AE summary will be generated presenting the frequency and percentage of subjects for the following:

- Any TEAE
- Any treatment related TEAE
- Any TEAE of grade 2 or higher
- Any treatment related TEAE of grade 2 or higher
- Any TEAE of grade 3 or higher
- Any treatment related TEAE of grade 3 or higher
- Any SAE
- Any treatment related SAE
- Any treatment related AE leading to early study drug discontinuation
- Any treatment related AE leading to early study discontinuation
- Any death

All AEs will be coded using MedDRA (version 24.1 or up). The TEAEs will also be summarized by system organ class (SOC), preferred term (PT), by severity and relationship to treatment. These TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, and AEs leading to study discontinuation.

9.2 Clinical Laboratory Evaluations

The following safety-related laboratory tests 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; neutrophils, lymphocytes, monocytes, eosinophils, and basophils
- Serum Chemistry: Alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), bilirubin (total and direct), blood urea nitrogen (BUN)/creatinine, creatinine, lipase, serum creatine kinase, bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, total protein, albumin, phosphate, calcium, and amylase
- Urinalysis: WBC, RBC, bacteria, epithelial cells, crystals, and casts.
- Coagulation: Prothrombin time, partial thromboplastin time, and international normalized ratio (INR)
- Other tests for female subjects: HCG; urine and serum

The hematology, serum chemistry, urinalysis, and coagulation tests will be performed at the time points pre-dose and post study-drug. Shift from baseline to worst post-baseline abnormality for these parameters will be presented using the Division of AIDS (DAIDS) standard. For parameters with both low and high ranges, separate summaries to low and high will be assessed.

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings. Abnormal laboratory results will be graded, where applicable, as follows:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ³ 7.3 to < LLN	pH < 7.3 without life- threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low	3.0 to < LLN	≥ 2.0 to < 3.0	< 2.0	NA

(g/dL; g/L)	30 to < LLN	≥ 20 to < 30	< 20	
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to £ 7.5	pH > 7.5 without life- threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High Report only one	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low	16.0 to < LLN	11.0 to < 16.0	8.0 to < 11.0	< 8.0
(mEq/L; mmol/L)	16.0 to < LLN	11.0 to < 16.0	8.0 to < 11.0	< 8.0
Bilirubin				
Direct Bilirubin1, High				
> 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High				
> 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High				
(mg/dL; mmol/L)				
≥ 7 days of age	10.6 to < 11.5	11.5 to < 12.5	12.5 to < 13.5	≥ 13.5
	2.65 to < 2.88	2.88 to < 3.13	3.13 to < 3.38	≥ 3.38
< 7 days of age	11.5 to < 12.4	12.4 to < 12.9	12.9 to < 13.5	≥ 13.5
	2.88 to < 3.10	3.10 to < 3.23	3.23 to < 3.38	≥ 3.38
Calcium (Ionized), High	> ULN to < 6.0	6.0 to < 6.4	6.4 to < 7.2	≥ 7.2
(mg/dL; mmol/L)	> ULN to < 1.5	1.5 to < 1.6	1.6 to < 1.8	≥ 1.8
Calcium, Low				
(mg/dL; mmol/L)				
≥ 7 days of age	7.8 to < 8.4	7.0 to < 7.8	6.1 to < 7.0	< 6.1
	1.95 to < 2.10	1.75 to < 1.95	1.53 to < 1.75	< 1.53
< 7 days of age	6.5 to < 7.5	6.0 to < 6.5	5.50 to < 6.0	< 5.50
	1.63 to < 1.88	1.50 to < 1.63	1.38 to < 1.50	< 1.38
Calcium (Ionized), Low	< LLN to 4.0	3.6 to < 4.0	3.2 to < 3.6	< 3.2
(mg/dL; mmol/L)	< LLN to 1.0	0.9 to < 1.0	0.8 to < 0.9	< 0.8
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN	> 1.8 to < 3.5	≥ 3.5 x ULN OR
*Report only one		OR Increase to 1.3 to	x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	Increase of ≥ 2.0 x participant's baseline
		< 1.5 x participant's baseline		
Creatinine Clearance 2	NA	< 90 to 60 ml/min or ml/min/1.73 m2	< 60 to 30 ml/min or ml/min/1.73 m2	< 30 ml/min or ml/min/1.73 m2 OR

or eGFR, Low		OR	OR	≥ 50% decrease from participant's baseline or dialysis needed
*Report only one		10 to < 30% decrease from participant's baseline	30 to < 50%	
			decrease from participant's baseline	
Glucose				
(mg/dL; mmol/L)				
Fasting, High	110 to 125	> 125 to 250	> 250 to 500	≥ 500
	6.11 to < 6.95	6.95 to < 13.89	13.89 to < 27.75	≥ 27.75
Nonfasting, High	116 to 160	> 160 to 250	> 250 to 500	≥ 500
	6.44 to < 8.89	8.89 to < 13.89	13.89 to < 27.75	≥ 27.75
Glucose, Low				
(mg/dL; mmol/L)				
≥ 1 month of age	55 to 64	40 to < 55	30 to < 40	< 30
	3.05 to <3.55	2.22 to < 3.05	1.67 to < 2.22	< 1.67
< 1 month of age	50 to 54	40 to < 50	30 to < 40	< 30
	2.78 to < 3.00	2.22 to < 2.78	1.67 to < 2.22	< 1.67
Lactate, High	ULN to < 2.0	³ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences
	x ULN without acidosis			
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders				
(mg/dL; mmol/L)				
Cholesterol, Fasting, High				
≥ 18 years of age				
	200 to < 240	240 to < 300	≥ 300	NA
	5.18 to < 6.19	6.19 to < 7.77	≥ 7.77	
< 18 years of age	170 to < 200	200 to < 300	≥ 300	NA
	4.40 to < 5.15	5.15 to < 7.77	≥ 7.77	
LDL, Fasting, High				
≥ 18 years of age	130 to < 160	160 to < 190	³ 190	NA

	3.37 to < 4.12	4.12 to < 4.90	³ 4.90	
> 2 to < 18 years of age	110 to < 130	130 to < 190	≥ 190	NA
	2.85 to < 3.34	3.34 to < 4.90	≥ 4.90	
Triglycerides, Fasting, High	150 to 300	>300 to 500	>500 to < 1,000	> 1,000
	1.71 to 3.42	>3.42 to 5.7	>5.7 to 11.4	> 11.4
Magnesium3, Low	1.2 to < 1.4	0.9 to < 1.2	0.6 to < 0.9	< 0.6
(mEq/L; mmol/L)	0.60 to < 0.70	0.45 to < 0.60	0.30 to < 0.45	< 0.30
Phosphate, Low				
(mg/dL; mmol/L)				
> 14 years of age	2.0 to < LLN	1.4 to < 2.0	1.0 to < 1.4	< 1.0
	0.65 to < LLN	0.45 to < 0.65	0.32 to < 0.45	< 0.32
1 to 14 years of age	3.0 to < 3.5	2.5 to < 3.0	1.5 to < 2.5	< 1.5
	0.97 to < 1.13	0.81 to < 0.97	0.48 to < 0.81	< 0.48
< 1 year of age	3.5 to < 4.5	2.5 to < 3.5	1.5 to < 2.5	< 1.5
	1.13 to < 1.45	0.81 to < 1.13	0.48 to < 0.81	< 0.48
Potassium, High	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
(mEq/L; mmol/L)	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Potassium, Low	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
(mEq/L; mmol/L)	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Sodium, High	146 to < 150	150 to < 154	154 to < 160	³ 160
(mEq/L; mmol/L)	146 to < 150	150 to < 154	154 to < 160	³ 160
Sodium, Low	130 to < 135	125 to < 130	121 to < 125	£ 120
(mEq/L; mmol/L)	130 to < 135	125 to < 130	121 to < 125	£ 120
Uric Acid, High	7.5 to < 10.0	10.0 to < 12.0	12.0 to < 15.0	≥ 15.0
(mg/dL; mmol/L)	0.45 to < 0.59	0.59 to < 0.71	0.71 to < 0.89	≥ 0.89
Absolute CD4+ Count,				
Low				
(cell/mm3; cells/L)				
> 5 years of age (not HIV infected)	300 to < 400	200 to < 300	100 to < 200	< 100
	300 to < 400	200 to < 300	100 to < 200	< 100
Absolute Lymphocyte Count, Low				
(cell/mm3; cells/L)				

> 5 years of age (not HIV infected)				
	600 to < 650	500 to < 600	350 to < 500	< 350
	0.600 x 109 to	0.500 x 109 to	0.350 x 109 to	< 0.350 x 109
	< 0.650 x 109	< 0.600 x 109	< 0.500 x 109	
Absolute Neutrophil Count (ANC), Low				
(cells/mm3; cells/L)				
> 7 days of age				
	800 to 1,000	600 to 799	400 to 599	< 400
	0.800 x 109 to 1.000	0.600 x 109 to 0.799	0.400 x 109 to 0.599	< 0.400 x 109
	x 109	x 109	x 109	
2 to 7 days of age	1,250 to 1,500	1,000 to 1,249	750 to 999	< 750
	1.250 x 109 to 1.500	1.000 x 109 to 1.249	0.750 x 109 to 0.999	< 0.750 x 109
	x 109	x 109	x 109	
≤ 1 day of age	4,000 to 5,000	3,000 to 3,999	1,500 to 2,999	< 1,500
	4.000 x 109 to	3.000 x 109 to 3.999	1.500 x 109 to 2.999	< 1.500 x 109
	5.000 x 109	x 109	x 109	
Fibrinogen, Decreased	100 to < 200	75 to < 100	50 to < 75	< 50
(mg/dL; g/L)	1.00 to < 2.00	0.75 to < 1.00	0.50 to < 0.75	< 0.50
	OR	OR	OR	OR
	0.75 to < 1.00 x LLN	≥ 0.50 to < 0.75 x LLN	0.25 to < 0.50 x LLN	< 0.25 x LLN
				OR Associated with gross bleeding
Hemoglobin4, Low				
(g/dL; mmol/L) 5				
≥ 13 years of age (male only)	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
	6.19 to 6.76	5.57 to < 6.19	4.34 to < 5.57	< 4.34
≥ 13 years of age (female only)	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
	5.88 to 6.48	5.25 to < 5.88	4.03 to < 5.25	< 4.03

57 days of age to < 13 years of age	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
(male and female)	5.88 to 6.48	5.25 to < 5.88	4.03 to < 5.25	< 4.03
36 to 56 days of age (male and female)	8.5 to 9.6	7.0 to < 8.5	6.0 to < 7.0	< 6.0
	5.26 to 5.99	4.32 to < 5.26	3.72 to < 4.32	< 3.72
22 to 35 days of age (male and female)	9.5 to 11.0	8.0 to < 9.5	6.7 to < 8.0	< 6.7
	5.88 to 6.86	4.94 to < 5.88	4.15 to < 4.94	< 4.15
8 to ≤ 21 days of age (male and female)	11.0 to 13.0	9.0 to < 11.0	8.0 to < 9.0	< 8.0
	6.81 to 8.10	5.57 to < 6.81	4.96 to < 5.57	< 4.96
≤ 7 days of age (male and female)	13.0 to 14.0	10.0 to < 13.0	9.0 to < 10.0	< 9.0
	8.05 to 8.72	6.19 to < 8.05	5.59 to < 6.19	< 5.59
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased	100,000 to	50,000 to	25,000 to	< 25,000
(cells/mm3; cells/L)	< 125,000	< 100,000	< 50,000	< 25.000 x 109
	100.000 x 109 to	50.000 x 109 to	25.000 x 109 to	
	< 125.000 x 109	< 100.000 x 109	< 50.000 x 109	
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased				
(cells/mm3; cells/L)				
> 7 days of age	2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
	2.000 x 109 to 2.499	1.500 x 109 to 1.999	1.000 x 109 to 1.499	< 1.000 x 109
	x 109	x 109	x 109	

≤ 7 days of age	5,500 to 6,999	4,000 to 5,499	2,500 to 3,999	< 2,500
	5.500 x 109 to 6.999	4.000 x 109 to 5.499	2.500 x 109 to 3.999	< 2.500 x 109
	x 109	x 109	x 109	
Glycosuria (random collection tested by dipstick)	Trace to 1+ or	2+ or > 250 to	> 2+ or > 500 mg	NA
	≤ 250 mg	≤ 500 mg		
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

1 Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.
2 Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.
3 To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
4 Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).
5 The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.
*Reminder: Choose the method that selects for the higher grade.

9.3 Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, and will be measured at the time points indicated in the schedule of assessments (refer to Section 3 of the protocol).

The number and proportion of normal and abnormal treatment-emergent vital signs will be summarized. Abnormalities are defined as:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Pulse rate	bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm

Variable	Unit	Low	High
Body temperature	C	Not applicable	≥ 38.3 °C AND change from baseline ≥ 1.1 °C
Weight	kg	Percent change from baseline ≤ -7.0 %	Percent change from baseline ≥ 7.0 %

All vital sign, body weight, and height measurements will be presented in a data listing. Where indicated, abnormalities will appear in the listing.

9.4 Physical Examination

All physical examination results will be presented in a data listing.

9.5 Electrocardiograms

Triplicate 12-lead ECG recordings will be performed at screening, on Day 6 and Day 28 after the subject has been in the supine position for at least 5 minutes. Mean of the triplicated measurements of the following will be reported: RR interval, PR interval, QRS width, QT interval, and Fridericia's corrected QT interval (QTcF). The investigator will perform an overall evaluation of the ECG and the recording will be reported as "normal", "abnormal clinically significant" or "abnormal not clinically significant". All ECG data will be summarized in a shift table and presented in a data listing.

10. Missing data handling

In general, observed data will be used in statistical analysis without imputation, unless missing data will jeopardize the integrity of the study or pose a problem in the validity of the analysis. A data-as-observed (DAO) approach will be used to evaluate the primary endpoint. Uncertain viral load measurements that are below the lower limit of quantification (LLOQ) will be set to 0.5 × LLOQ in the viral load summaries and indicated as BLQ in the listings. If subjects withdraw early, the outcome measure up to point of study withdrawal will be used.

Impact of missing data will be assessed, and ad-hoc sensitivity analysis will be performed when deemed appropriate. No imputation is planned for the primary efficacy analysis, as the study allows replacement when a subject withdraws without any post-baseline virology data and a mixed model will be used. If at a particular time point, the amount of missing data in the AT-752 arm is greater than 10% due to dropout, the impact will be assessed. In this case, an ad-hoc sensitivity analysis using multiple imputations will be performed using the Markov chain Monte Carlo (MCMC) method to impute non-monotone missing data, and a copy reference (i.e. placebo) approach to impute monotonic missing data in the AT-752 arm.

For safety data, missing and partial dates will be programmatically handled according to the following standards: if the day of the month is missing for any date used in a calculation, the 1st of

the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of resolution cannot be prior to date of onset; if replacing resolution date with the 1st of the month results in a negative duration, the resolution date will be set to the onset date). In this case, the date resulting in 0 time duration will be used. These standards are also used if both month and day are missing (Jan 1 unless negative time duration, durations will be reset to 1 day).

11. Pharmacokinetics

Plasma PK concentrations for CCI , AT-551, AT-229, AT-219 and AT-273 will be summarized for each nominal scheduled collection time. Summaries will include descriptive statistics (number of subjects, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum) and the number/percentage of samples reported as below the limit of quantification (BLQ).

All PK listings and individual concentration-time profiles will be presented for the AT-752 treated safety population. Plasma concentration versus actual time profiles for each subject will be presented graphically by treatment using a semi-logarithmic scale. The mean plasma concentration versus scheduled time profiles will be presented graphically by treatment using a semi-logarithmic scale.

11.1 Data handling

Data rounding specifications for PK data are documented in the PK table list figure (TLF) shells.

Plasma concentrations that are BLQ will be treated as zero for calculation of concentration descriptive statistics; if <3 values are above the lower limit of quantification (LLOQ) at one time point, the arithmetic mean, SD, and CV will not be reported at that time point. For PK parameter analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing. For the estimation of geometric mean and geometric CVs, all BLQ values will be set to missing.

11.2 Plasma Pharmacokinetic Parameters

Plasma parameters derived from plasma samples using non-compartmental analysis with Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) or SAS Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina), as appropriate.

PK samples will be obtained on Day 1 (predose) and at 24 hours after Dose 1(before Dose 4 for TID dosing and before Dose 3 for BID dosing). For TID dosing, intensive PK 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, intensive PK 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, 7, based on site/patient convenience. For blood samples (both TID and BID dosing), there is a ±10-minute window for time points ≤4 hour and a ±15 minute window for the time points between 4 and 24 hours.

Noncompartmental analysis will be used to estimate the following PK parameters, when applicable and if data permit: CCI, AT-551, AT-229, AT-219 and AT273:

C_{trough}	Observed trough (predose) concentration (TID on Dose 7, BID on Dose 5). AT-273
C_{max}	Maximum observed concentration.
T_{max}	Time of maximum observed concentration.
AUC_{last}	AUC from time 0 to the last measurable observed concentration (Ct), calculated using the linear trapezoidal rule.
AUC_{tau}	AUC within a dosing interval, calculated using the linear trapezoidal rule.

For each PK parameter, only subjects with sufficient concentration data to support accurate estimation of at the PK parameter will be included the summary.

Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations will be included in the analysis (including concentrations collected outside predefined collection windows). Predose concentrations collected prior to subsequent doses will be included in the PK parameter calculation for the previous dose, where appropriate.

PK parameters of CCI, AT-551, AT-229, AT-219 and AT-273 (plasma) will be summarized by treatment and ethnicity using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum). T_{max} will be summarized using number of observations, median, minimum, and maximum values.

12. Pharmacodynamics

Change from baseline in DENV viral load (as measured by viral titer) from baseline will be analyzed with repeated measures mixed model using the method of restricted maximum likelihood (REML). The model will include baseline viral load, treatment, time, and treatment-by-time interaction as fixed factors. An unstructured covariance matrix will be specified for the repeated statement. In case a mixed model with unstructured (UN) covariance matrix fails to converge, a compound symmetry (CS) structure will be used as an alternative. If neither of these converges, independent (ID) structure will be used. The treatment group least squares mean (LSM) estimates for mean change from baseline and treatment group differences at each time point, with 80% CI, 95% CI and p-value will

be presented. If none of the covariance structures converge, only descriptive summaries will be included.

Area under the change of the log 10-tranformed viral load curve (AUC) from first dose to the end of treatment (Day 5-6) and to study end (Day 28) will be presented by treatment.

AUC_{D5} and AUC_{D28} refer to area under the log 10-tranformed viral load curve (AUC) from first dose to the end of treatment (Day 5) and to study end (Day 28) respectively. The following rules will be followed for the area under the curve derivation.

- A time-scaled trapezoidal rule will be used for AUC calculation.
- AUC will be calculated from the log 10-tranformed viral load curve connecting baseline or the first available viral load measurement time point before Day 5 till Day 5 for AUC_{D5} Similarly, connecting the baseline or the first available viral load measurement time point before Day 28 till Day 28 for AUC_{D28}
- Subjects with missing Day 5 measurements will have Day 5 viral load imputed from last and next available viral loads by linear interpolation for AUC_{D5} calculation. If viral load measurement is missing for Day 5 and all subsequent measurement days beyond Day 5, the subject will not have AUC_{D5} calculated and will be excluded from AUC analyses.
- Subjects with missing Day 28 measurements will not have AUC_{D28} calculated and will be excluded from AUC analyses.

Intermediate missing log 10-tranformed viral loads (between baseline and the last day) will be linearly interpolated using the last and next available viral loads for AUC calculation for both AUC_{D5} and AUC_{D28}. Subjects with intermediate missing values will be included in AUC analysis.

Time to viral load (as measured by DENV RNA and viral titre) or NS1 clearance, defined as time to first of 2 consecutive results of undetectable viral load or NS1, will be described using Kaplan-Meier methods. The median time to viral clearance and the estimated proportions of patients with viral clearance will be summarized by treatment group. Patients who do not receive a record of a negative test result by RT-PCR/viral titre or NS1 antigen assay by the last observation timepoint will be treated as censored at the final scheduled evaluation time point.

Subgroup analysis by DENV serotype will be carried out for the following endpoints: change of DENV viral load (as measured by DENV RNA and viral titre) from baseline, viral load AUC, time to viral load or NS1 clearance. Descriptive statistics (N, mean, standard deviation, median, minimum and maximum, and 95% CI) will be presented by treatment group.

Number and percentage of subjects with treatment-emergent amino acid substitutions in DENV NS5 gene will be compared between the treatment groups (chi-squared test).

Duration of fever is the sum of fever episode durations where fever episode duration is defined as the time from first fever measurement (either at baseline or following a period without fever) to the next measurement without fever. If the last episode has not resolved, duration for that episode will be

censored at the time of the last temperature measurement. Treatments will be compared by log-rank test.

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). Data will be presented in descriptive statistics by treatment.

Exploratory analyses may be performed to evaluate exposure-response relationship. The relationship between the exposure of AT-752 (AT-281 and its metabolites AT-551, AT-229, and AT-273) and DENV viral load may be explored using graphical displays. Scatter plots of drug exposure versus change in DENC viral load will be provided.

13. Interim Analysis

No formal interim analysis was planned in the study. As this is an early phase study, the Sponsor may perform unblinded interim reviews of the data during the course of the study.

14. Changes in the Planned Analysis

There are no changes to the planned analyses described in the protocol.

15. References

Schedule of Events

Assessment	**Screening**	**Treatment Period**			**Follow-up**				
		Day 1	**Days 2-4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 14±1**	**Day 28 ±3/ EOS (Early Termination)**
Visit Type	**Site**	**Site**	**Site or Mobile**	**Site or Mobile**	**Site**	**Site or Mobile**	**Site or Mobile**	**Site or Mobile**	**Site**
Eligibility criteria	X								
Informed consent[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 (Day 28 only)
NS1 antigen test	X	X	X	X	X	X	X	X	X (Day 28 only)
Plasma Biomarker	X	X	Day 2, 4		X		X	X	X (Day 28 only)
Adverse events[k]	X	X	X	X	X	X	X	X	X
Randomization	Prior to dosing								
Study drug administration		X	X	X					
Accountability of returned drug, and review of patient diary					X				X (Early Termination only)

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

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

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.

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).

Hematology/ chemistry/ coagulation to include complete blood count (CBC) including white blood cell (WBC) count with differential count, red blood cell (RBC) count, platelet count, hemoglobin, hematocrit, and RBC indices; aspartate transaminase (AST), alanine aminotransferase (ALT), total and direct bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, serum creatine kinase, lipase, bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, total protein, albumin, phosphate, calcium, and amylase; international normalized ratio (INR), prothrombin time, and partial thromboplastin time. Urinalysis will be performed with microscopy at indicated visits but treatment with study drug may begin before the screening results have been obtained unless medically required to establish eligibility (at investigator's discretion). Additional urinalysis may be performed as clinically indicated.

One-time retests of individual screening laboratory parameters or assessments may be permitted in certain scenarios. Such scenarios may include lab processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting screening laboratory results. Standard of care laboratory results prior to informed consent are accepted if performed within 24 hours of screening.

SARS-CoV-2 rapid test performed at screening and Day 6. RIDT performed only at screening.

A dipstick pregnancy test is required at screening. Additional pregnancy tests may be performed locally as clinically indicated.

Rapid point of care (POC) test for DENV NS1 antigen. See Protocol Section 3.1.4 for details about assay timing.

Pharmacokinetic (PK) plasma samples will be collected on Day 1 at time 0 (pre-dose; before the first dose on Day 1) and 24 hours after Dose 1. For TID dosing, samples will be obtained before Dose 7 and 0.5, 1, 2, 4, and 6 hours after Dose 7. This serial PK sampling for TID dosing may be done for Dose 7, 8, or 9, based on site/patient convenience. For BID dosing, samples will be obtained before Dose 5 and 0.5, 1, 2, 4, 6, and 8 hours after Dose 5. This serial PK sampling for BID dosing may be done for Dose 5, 6, or 7, based on site/patient convenience. For blood samples, a ± 10-minute window for time points ≤4 hours; ± 15 minute for time points between 4 and 24 hours. PK samples will also be obtained at any early study discontinuation visits. The timing of these PK samples relative to the last 2 (most recent) doses will be recorded. See Protocol Section 3.1.4.

Subjects can begin treatment with study drug before the DENV-serotype results are obtained.

Measurement of plasma viremia by viral titre and using a serotype-specific, real-time reverse transcription polymerase chain reaction (RT-PCR) assay. Subjects can begin treatment before the viral load results are obtained. See Protocol Section 3.1.4 for details about the timing of this assay.

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.

After subjects are confirmed eligible at screening, randomization and the initial dosing should occur within 24 hours, the initial dose should be given on the same day as screening, if possible. TID dosing at screening/Day 1 can begin in the morning, at mid-day, or in the evening (see Protocol Section 3.1.2. BID dosing on Screening/Day 1 can begin in the morning or the evening (See Protocol 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.

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.