Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2a, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Antiviral Activity, Safety and Tolerability, and Pharmacokinetics of JNJ-64281802 in Participants With Confirmed Dengue Fever.

Protocol 64281802DNG2003; Phase 2
AMENDMENT 6

JNJ-64281802

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

Status: Approved
Date: 06 June 2022
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-ERI-205547480, 9.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Date
Amendment 6	06 June 2022
Amendment 5	28 February 2022
Amendment 4	22 November 2021
Amendment 3	26 March 2021
Amendment 2	08 September 2020
Amendment 1	4 August 2020
Original Protocol	19 June 2020

Amendment 6 (06 June 2022)

Overall Rationale for the Amendment: The Sponsor decided to include an additional country for the conduct of the trial (Vietnam) and to introduce a CCI formulation of the study intervention for use in newly recruited participants, when it becomes locally available.

In addition, the protocol was amended to decrease the lower age limit to 18 years of age depending on legal age of consent in the country, to increase the time window from randomization to the first dose from 30 minutes to CCI minutes, to allow an option of ambulatory visits on Days 3, 4, 5, and 6, to introduce an additional exclusion criterion to exclude patients with past/prior dengue infections, and to include an optional reduction of blood sample volume for cellular immunity.

Some minor corrections and/or clarifications were addressed as outlined in the table below.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 2. Introduction 2.1. Study rationale 4.1. Overall design 4.3. Justification for dose	Vietnam has been added as a second country.	To facilitate recruitment.
1.1. Synopsis 1.2. Schema 1.3. Schedule of Activities 4.1. Overall Design 4.3. Justification for dose 6.1. Study Intervention(s) Administered	The use of the CCI formulation of the study intervention and related dosing regimen have been added.	To ensure provision of the study drug to sites after expiry date of the currently used CCI formulation and to facilitate operational and logistic aspects of the study.
1.1 Synopsis 4.1. Overall Design 5.1. Inclusion Criteria	The lower age limit for inclusion in the study has been decreased to 18 years of age depending on the legal age of consent in the country.	To accommodate the investigator's request to be able to include younger adult patients in countries where the legal age of consent is lower than 21 years.

Section number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	A criterion to exclude patients with past/prior laboratory-confirmed dengue infection (any PCR, NS1, IgG/IgM seroconversion) was added.	To ensure adequate numbers of primary infected participants are enrolled in accordance with the assumptions made in the sample size section.
1.1. Synopsis 1.3. Schedule of Activities 4.1. Overall Design	The time window from randomization to the first dose administration has been increased from 30 minutes to CCI minutes.	To accommodate the investigator's request and facilitate operational aspects of the study.
1.1. Synopsis 4.1. Overall design 6.3. Measures to Minimize Bias: Randomization and Blinding	Wording on randomization has been updated to include stratification by country.	An additional stratification factor "by country" has been included, since the study will now be conducted in more than one country.
1.1. Synopsis 8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting	All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated main study ICF is obtained until completion of the participant's last study related. For participants with only a signed pre-screening (diagnostic) ICF, no AEs will be reported.	To emphasize that a pre-screening (diagnostic) ICF only consents for the diagnostic test, and no other study related assessments.
1.3. Schedule of Activities 8. Study assessments and procedures	An option to reduce the blood sample volume for cellular immunity (PBMC) from 30 mL to 10 mL at Day 28 has been added	To accommodate the investigator's request and to align with local regulations in Vietnam.
2.1. Study rationale	Information on prevalence of dengue virus in Vietnam has been added.	Added because of addition of Vietnam as participating country.
1.1. Synopsis 1.2. Schema 1.3. Schedule of Activities 4.1. Overall design 6.1. Study Intervention(s) Administered	An option for ambulatory visits on Days 3, 4, 5, and 6 has been added.	To accommodate the investigator's request.
9.4. Statistical Analyses	An option for exploratory subgroup analysis for the different drug formulations used in the trial has been added.	To provide an option of additional analysis following addition of the CCI formulation.
4.1. Overall design	Text added: "The population will include participants with a primary and a non-primary or secondary infection. The difference between the 2 subpopulations will be determined before database lock and will be based on the IgG profile."	For clarification
Throughout the protocol	Minor updates, corrections, or additions have been made.	Correction, clarification, and consistency.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2a, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Antiviral Activity, Safety and Tolerability, and Pharmacokinetics of JNJ-64281802 in Participants With Confirmed Dengue Fever.

JNJ-64281802 is a novel anti-dengue small molecule targeting DENV non-structural protein (NS)4B. It has shown potent antiviral activity across all 4 DENV serotypes in preclinical studies. A Phase 1 first-in-human study 64281802DNG1001 (further referred to as DNG1001) to assess the safety, tolerability, and pharmacokinetics (PK) of increasing single and multiple oral doses of JNJ-64281802 in healthy adult participants has been performed.

This is a Phase 2a, multicenter study to be conducted in Singapore and Vietnam. The aim of the study is to examine the antiviral activity, PK, and safety and tolerability of JNJ-64281802, compared to placebo, and to evaluate the improvement in clinical signs and symptoms with the administration of JNJ-64281802 for the treatment of dengue.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Investigate the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV RNA in primary DENV infection	• Area under the log_{10}-transformed DENV RNA viral load (log_{10} VL) curve from baseline until Day 5 ($AUC_{D1\text{-}D5}$ [log_{10}VL]).
Secondary	
• Assess the safety and tolerability of JNJ-64281802 in primary and secondary DENV infection	• AEs • ECGs • physical examinations • vital signs • clinical laboratory assessments
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on other virological endpoints in primary DENV infection	• Virologic endpoints derived from the DENV RNA, including – Occurrence of detectable DENV RNA at each time point in primary DENV infection – Time to undetectable DENV RNA in primary DENV infection
• Evaluate the PK of JNJ-64281802	• PK parameters for JNJ-64281802
Exploratory	
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on DENV infectious viral titer (further referred to as viremia) in primary DENV infection	• Virologic endpoints derived from viremia, including – Area under the log_{10}-transformed viremia curve from baseline until Day 5 in primary DENV infection – Occurrence of detectable viremia at each timepoint in primary DENV infection – Time to undetectable viremia in primary DENV infection

Objectives	Endpoints
• To explore the relationship between the exposure and antiviral activity of JNJ-64281802	• PK (plasma concentrations or exposure parameters) of JNJ-64281802 • Area under the log10-transformed viremia or DENV RNA viral load
• Investigate the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV RNA in secondary DENV infections and in all DENV infections	• Virologic endpoints derived from the DENV RNA, viral load, including – Area under the log_{10}-transformed DENV RNA viral load curve from baseline until Day 5, in secondary DENV infection – Occurrence of detectable DENV RNA at each time point in secondary DENV infection – Time to undetectable DENV RNA in secondary DENV infection
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on viremia in secondary DENV infections and in all DENV infections	• Virologic endpoints derived from viremia, including – Area under the log_{10}-transformed viremia curve from baseline until Day 5 in secondary DENV infection – Occurrence of detectable viremia at each timepoint in secondary DENV infection – Time to undetectable viremia in secondary DENV infection
• Investigate the effect of JNJ-64281802 versus placebo on the change in hematology values over time (leucocytes, platelets, and hematocrit)	• The maximal decrease from baseline (per participant) observed in platelet counts from Day 2 to Day 5 • The maximal decrease from baseline (per participant) observed in leucocyte counts from Day 2 to Day 5 • The maximal increase from baseline (per participant) observed in hematocrit concentration from Day 2 to Day 5
• Investigate the effect of JNJ-64281802 versus placebo on the immunological profile	• The occurrence and magnitude of anti-DENV total IgM and IgG antibody titers
• To explore the effect of JNJ-64281802 versus placebo on DENV-related clinical signs and symptoms	• Time to resolution of dengue signs and symptoms • Severity of dengue signs and symptoms
• To assess changes in the viral genome sequence (with a focus on NS4B) in participants with detectable DENV RNA	• Changes in the viral genome sequence at and between first viral isolation and last viral isolation
• To explore the DENV NS1 serum protein levels	• Occurrence and magnitude of DENV NS1 serum protein levels
• To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802	• HLA genotyping and pharmacogenomic analyses
The following additional exploratory objectives may be evaluated at the discretion of the sponsor: • Investigate the effect of JNJ-64281802 versus placebo on immunological profile based on occurrence and magnitude of anti-DENV cellular immune responses	

Objectives	Endpoints
• To explore changes in serum protein levels (including cytokines) • To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802 based on biomarker analysis via transcriptional profiling of host RNA • The occurrence and magnitude of an anti-DENV neutralizing antibody response	

Abbreviation key: AE(s) adverse event(s), AUC area under the curve, DENV dengue virus, ECG: electrocardiogram, HLA human leukocyte antigen, Ig Immunoglobulin, NS non structural, PK pharmacokinetic, RNA ribonucleic acid, VL viral load

Hypothesis

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to reduction in viral load in participants with a primary DENV infection, as measured by area under the log_{10}-transformed DENV RNA viral load curve from baseline until Day 5.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2a interventional study in participants aged ≥18 or ≥21 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤60 years. Participants who report with an onset of fever of <48-hour duration at screening and who test positive for DENV infection by the NS1 assay will be randomized in the study. Randomization will be stratified by country and by duration of dengue symptoms from onset of fever as reported by the participant until the time of randomization (≤24 hours and >24 hours).

The population will include participants with a primary and a non-primary or secondary infection. The difference between the 2 subpopulations will be determined before database lock and will be based on the IgG profile.

There are three sequential phases in the study: screening/baseline, double-blind treatment and follow-up. Study participants will complete the screening/baseline visit on Day 0 (predose), followed by a double-blind treatment phase from Day 1 to Day 6 or Day 9 (for participants with dengue warning symptoms). During the double-blind treatment period, participants will be admitted to an inpatient facility. At the investigator's discretion, ambulatory visits instead of inpatient treatment can be allowed at Days 3, 4, 5, and 6. All participants will be followed up for a total of 6 months after the first dosing day. The entire study duration for each participant will be approximately 6 months (±4 days). The participants will complete the study after having completed the final remote follow-up assessment planned 6 months (±4 days) after having received the first dose of study intervention, unless ongoing adverse events (AEs) require monitoring.

Mobile clinical teams consisting of trained and delegated site staff (eg, nurses, clinical research coordinators [CRCs]) will visit the clinics and communities to sensitize and pre-screen potential study participants and play an active role in participant recruitment. Individuals with a suspected DENV infection will be asked to undergo an NS1 rapid test after signing a pre-screening ICF during an ambulatory visit at a health care facility organized by the mobile clinical teams.

The study sites will be open to receive referrals of participants who have consulted a health care facility (eg, clinic/polyclinic, hospital) or practitioner (eg, general practitioner [GP], medical doctor [MD], nurse) with an onset of fever within the last 48 hours, as reported by the participant, and who tested positive for DENV infection by the NS1 assay at the health care facility. Individuals who test positive during an ambulatory visit or as part of Standard of Care DENV NS1 rapid testing, will be referred to the study site to further coordinate informed consent signing and completion of eligibility assessments. In addition, participants may also report directly to the study site. Participants identified at the study site with an onset of fever as reported by the participant within the last 48 hours, and who test positive for DENV infection by the NS1 assay performed at the site after signing the ICF, will undergo eligibility assessment.

The screening/baseline assessments are to be completed as quickly as possible at the study site. Participants who successfully meet all inclusion criteria and none of the exclusion criteria, will be enrolled and admitted to an inpatient facility. The participants will then be randomized to receive placebo or JNJ-64281802. CCI [redacted] Results of screening assessments need to be documented in the electronic case report form (eCRF).

An internal Data Review Committee (DRC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

A planned target of 150 male and female participants will be randomly assigned in a ratio of 1:1 to receive JNJ-64281802 or placebo in this study with approximately 75 participants planned per intervention group. The sample size can be revised after an interim analysis on the proportion of primary versus secondary DENV infections.

INTERVENTION GROUPS AND DURATION

JNJ-64281802 (in either CCI [redacted] formulation) or matching placebo will be administered according to the following dosing regimens:

CCI [redacted]

The CCI [redacted] formulation will be introduced for use in newly recruited participants, when it becomes locally available.

The CCI [redacted] formulation was selected based on the results of study 64281802DNG1006, CCI [redacted]

When dosed in fasted condition in 16 healthy volunteers, the JNJ-64281802 C_{max} and AUC_{∞} were similar between CCI [redacted] and CCI [redacted], with geometric mean ratios of 1.06 and 1.00, respectively. The effect of food on JNJ-64281802 exposure when formulated as CCI [redacted] tablet was dose dependent. When administered with a standardized breakfast, JNJ-64281802 C_{max} was increased by 33%, 76%, and 178% compared to fasted conditions for a single dose of 50 mg, 200 mg, and 800 mg, respectively. For AUC_{∞} this increase was 12%, 69%, and 143%, respectively.

CCI [redacted]

The participants will stay at an inpatient facility from Day 1 to Day 6, with an option of ambulatory visits on Days 3, 4, 5, and 6 at the investigator's discretion. Daily clinical monitoring will be conducted, and blood samples will be collected. Oral intake of food and fluids will be recorded on Days 1, 2, 3, 4, and 5 of dosing.

The participants will be discharged from the inpatient facility on Day 6 (on Day 2 for ambulatory visits) after the assessments have taken place and given their clinical status is satisfactory for discharge in the opinion of the investigator. Participants who develop dengue warning symptoms as defined by the World Health Organization (WHO)[a] will remain at the inpatient facility after Study Day 6 for an additional 3 days and planned outpatient assessments will be performed by the study team members, where required. Patients with severe dengue (dengue hemorrhagic fever [DHF] or dengue shock syndrome [DSS]), or participants who are hemodynamically unstable or require interventions, can be transferred to a hospital at any time during the inpatient stay, at the investigator's discretion. Participants with severe dengue or dengue warning symptoms after Study Day 9 will be moved to a hospital. After discharge, the participants will be asked to return on Days 14, 21, and 28 (±2 days) for assessments after which remote visits are scheduled every 2 weeks for the assessment of possible DENV infection associated AEs, up to 6 months after the first study intervention intake.

[a] World Health Organization: Dengue. Guidelines for diagnosis, treatment, prevention and control 2009

Description of Interventions

Arm Name	Intervention	Placebo
Intervention Name	JNJ-64281802	Placebo
Type	Drug	Placebo
Dose Formulation	CCI [redacted]	
Unit Dose Strength(s)		
Dosage Level(s)		
Route of Administration	Oral	Oral
Use	Experimental	Placebo
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. CCI [redacted]	CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. CCI [redacted]

Arm Name	Intervention	Placebo
	CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container.	CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container.
Food/Fasting requirement	CCI [redacted]	

ANTIVIRAL ACTIVITY EVALUATIONS

Antiviral activity will be assessed using (i) DENV RNA levels, (ii) Levels of infectious dengue virus (viremia) and (iii) Levels of DENV NS1 protein in serum. Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of the DENV infection and antiviral activity of the study intervention.

DENV RNA levels will be assessed using a validated quantitative DENV RT-PCR assay.

DENV viremia (ie, level of infectious DENV) will be determined using an assay for infectious virus quantification such as a plaque assay.

In addition, antiviral activity will be explored by assessing NS1 protein using an NS1 test. Confirmation of DENV infection will be done retrospectively using qualitative PCR after screening.

Additionally, blood samples will be obtained for the assessment of clinical endpoints (leukocyte count, platelet count, and hematocrit concentration).

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be used to evaluate the PK of JNJ-64281802. Plasma collected for PK may additionally be used to evaluate safety, pharmacokinetic (plasma protein binding, metabolites) or antiviral activity aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

BIOMARKER EVALUATIONS

The study includes collection of blood samples for exploratory analysis.

Samples for host RNA might be used for transcriptional profiling for example using microarray technology. Serum samples for protein analyses might be analyzed using assays such as ELISA or Luminex.

Samples can only be used for research related to JNJ-64281802 or DENV infection or may be used to develop tests/assays related to JNJ-64281802 or DENV infection.

IMMUNE ASSESSMENTS

Blood samples will be obtained for the assessment of antibody response. Anti-DENV IgG and IgM will be measured using commercial ELISA and the IgG pattern will be used to make a distinction between primary and secondary dengue infection. Presence of neutralizing antibodies (IgG and IgM) against DENV will be determined using an assay such as flow cytometry-based neutralization assay.

Peripheral blood mononuclear cell (PBMC) samples may be analyzed in a subset of participants to assess DENV-specific T and B cell immune responses by assays such as enzyme-linked immunospot assay (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with DENV-specific antigens. ELISpot detects T cells that secrete gamma interferon (IFN-γ) or B cells that secreted IgG and/or IgM in response to an antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ T cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs by flow cytometry or other methods including but not limited to CyTOF, to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research related to DENV infection or JNJ-64281802 (safety/antiviral activity).

VIRAL GENOME SEQUENCING

Viral genome sequencing analysis will be performed by sequencing the NS4B gene and other regions of the DENV genome (if warranted) to characterize emerging DENV variants associated with resistance to

JNJ-64281802.

Sequencing of the DENV genome will be performed to monitor DENV variants at selected timepoints at the discretion of the sponsor's virologist.

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of DENV infection and antiviral activity and safety of JNJ-64281802.

PHARMACOGENOMIC (DNA) EVALUATIONS

Human Leucocyte Antigen Typing and Pharmacogenomic Assessments

One blood sample for human leucocyte antigen (HLA) typing and for pharmacogenomics (DNA) research will be taken, preferably at baseline (ie, before first dose of study intervention). This sample can be used to determine the HLA type of the participant. In addition, this sample can be used to investigate the potential association of genetic factors with PK, antiviral activity or safety of JNJ-64281802 or the DENV infection.

These analyses may be conducted under the supervision of the sponsor and may be reported separately from the main study report. If necessary, the sample may be collected at a later time point without constituting a protocol deviation.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event Section of the eCRF and in the source documentation.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution (return to baseline) or until a clinically stable condition is reached (to be agreed upon with the sponsor) or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated main study ICF is obtained until completion of the participant's last study-related procedure. For participants with only a signed pre-screening (diagnostic) ICF (ie, for whom consent was not given to enroll in the main study by signing the main ICF), no AEs will be reported.

The study will include evaluations of AEs, Clinical laboratory tests (including prothrombin time [PT], international normalized ratio [INR], and activated partial thromboplastin time [APTT] as measures of effects on blood coagulation), ECGs, vital signs and physical examination.

Additionally, dengue signs and symptoms will be monitored throughout the study.

STATISTICAL METHODS

The primary analysis will be performed when all participants reached Day 28 or discontinued earlier. The final analysis will be performed when all participants completed the study or discontinued earlier.

Sample Size Determination:

The study will recruit in total 150 participants, with the primary objective of investigating the antiviral activity of JNJ-64281802 versus placebo based on DENV RNA in primary DENV infection and with a secondary objective to describe the safety and tolerability of JNJ-64281802 in participants with DENV infection The sample size can be revised after an interim analysis on the proportion of primary versus

secondary DENV infections.

For the objective of antiviral activity in participants with a primary DENV infection, the hypothesis is that the intervention effect is superior to placebo as measured on the DENV RNA log_{10} viral load curve from baseline until Day 5.

To assess sample size requirements for this hypothesis, data of 47 DENV RNA curves were estimated similar to the DENV RNA curves graphically presented in the balapiravir trial. All curves were considered as balapiravir did not have an effect on the viral load. A limit of detection of 2.3 log copies/mL was assumed. Although the majority of the population included in the balapiravir trial suffered from a secondary infection, these estimated DENV RNA curves were considered representative for a primary infected dengue population. As the clearance of DENV RNA occurs earlier and faster in participants with secondary dengue, this is a conservative assumption.

The 47 estimated DENV RNA curves were used to calculate the means, standard deviations, and correlations of the log_{10} viral loads over time. These calculated values were thereafter used to simulate 10,000 trials, each with a sample size of 80 participants. A treatment effect of 0.30 log_{10} copies/mL per day DENV RNA clearance on top of placebo, or two-fold reduction of the viral load was applied. Based on these 10,000 simulated trials and using a general linear model with treatment regimen as fixed factor and baseline log_{10} viral load as a covariate, a sample size of 80 participants (40 per group) was estimated to provide a power of at least 80% at the one-sided 5% significance level to detect an intervention effect of 0.30 log_{10} copies/day additional DENV RNA clearance when compared to placebo.

The specificity of the DENV NS1 testing at baseline is estimated to be 98% which entails that 2% of participants that will be enrolled will not be evaluable for efficacy. Based on literature, it is estimated that approximately 60% of the total population will have a primary infection. Furthermore, it is anticipated that approximately 4% of the enrolled participants drop-out for other reasons. The study will therefore need to recruit a total of 150 participants in order to achieve a sample of 84 participants to achieve >80% power on the primary hypothesis.

For the objective of safety assessment, the probability was calculated to observe an (S)AE that has a true incidence of 1% which would be 53% with a total sample size of 75 participants on active treatment; the probability to observe an (S)AE with a true incidence of 0.1%, 0.5% and 0.8% is 7%, 31% and 45%, respectively.

Antiviral Activity Analysis

Primary Endpoint: The difference in area under the log_{10}-transformed DENV RNA viral load curves from immediately prior to first dose (baseline) until Day 5 for JNJ-64281802 versus placebo dosing will be derived from a mixed model with treatment regimen and the stratification factors as fixed factors and baseline log_{10} viral load as a covariate, calculating least square mean differences, including the 90% 2-sided confidence intervals in the intent-to-treat infected (ITT-i) population with a primary dengue infection based on IgG profile.

Secondary and Exploratory Endpoints: Descriptive statistics and mean (and standard error) graphs will be shown for the log_{10} DENV RNA and viremia actual values and changes from baseline over time in participants with primary DENV infection.

In participants with primary DENV infection, the proportion of participants within the DENV RNA and viremia categories (≥lower limit of quantification [LLOQ], <LLOQ target detected, and <limit of detection [LOD] target not detected) will be shown in a frequency tabulation per analysis time point.

Time to undetectable DENV RNA/viremia will be analysed using Kaplan-Meier estimates analysis. A summary table including number of participants with primary DENV infection included in the analysis, number of participants censored, 25^{th} and 75^{th} percentiles and median time-to event, with 95% confidence

intervals based on log-log transformation method, will be presented. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by treatment.

Descriptive statistics will also be used to describe the IgM and IgG response. The proportion of participants with antibody positivity and the titer and timing of the antibody response will be determined. Descriptive statistics will include sample size, mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum.

Safety Analysis

Safety data will be presented descriptively. No statistical testing of safety data is planned.

Immune Analysis

Humoral Immune Analysis: Descriptive statistics will be used to describe the neutralizing antibody response. The proportion of participants with antibody positivity, including neutralizing antibodies for all 4 DENV serotypes, and the titer and timing of the antibody response will be determined. Descriptive statistics will include sample size, mean, SD, CV, geometric mean, median, minimum, and maximum.

Cellular Immune Analyses: Descriptive statistics will be used to describe the magnitude of the IFN-γ T cell response or the CD4+ and CD8+ T cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any antigen) or B cell response as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) will also be tabulated for PBMCs during the dosing and on-site follow-up phase (Day 28, optional). The proportion of participants with positive responses based on the magnitude of the IFN-γ T cell response or the CD4+ or CD8+ T cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the antigens as defined by ELISpot and/or ICS, respectively, or B cells that secrete IgG and/or IgM will be determined.

Pharmacokinetic Analysis

All participants having received at least one dose of study intervention and having at least one PK parameter value will be included in the PK analysis. All participants having received at least one dose of study intervention and having at least one plasma concentration data value after administration will be included in the descriptive statistics.

Descriptive statistics will be calculated for the plasma concentrations of JNJ-64281802 and for the derived PK parameters, as applicable. Statistics include sample size (n), mean, SD, CV, geometric mean, median, minimum, and maximum.

For each participant, plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis including various transformations in order to get a general overview.

Special attention will be paid to the plasma concentrations and PK parameters of those participants who have discontinued the study for an AE, or who experienced an AE of at least grade 3, or a serious adverse event (SAE).

Relationships of PK parameters for JNJ-64281802 as applicable, with selected antiviral activity and with selected safety endpoints may be evaluated, applying graphical tools and, if feasible, statistical models.

Biomarker Analysis

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between participants. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented in the clinical study report or a separate report.

Viral Genome Sequence Analysis

The results of DENV viral genome sequencing will be evaluated by the sponsor virologist. Relevant changes in the DENV genome will be tabulated and described for participants with detectable DENV RNA during the study period.

Pharmacogenomic Analysis

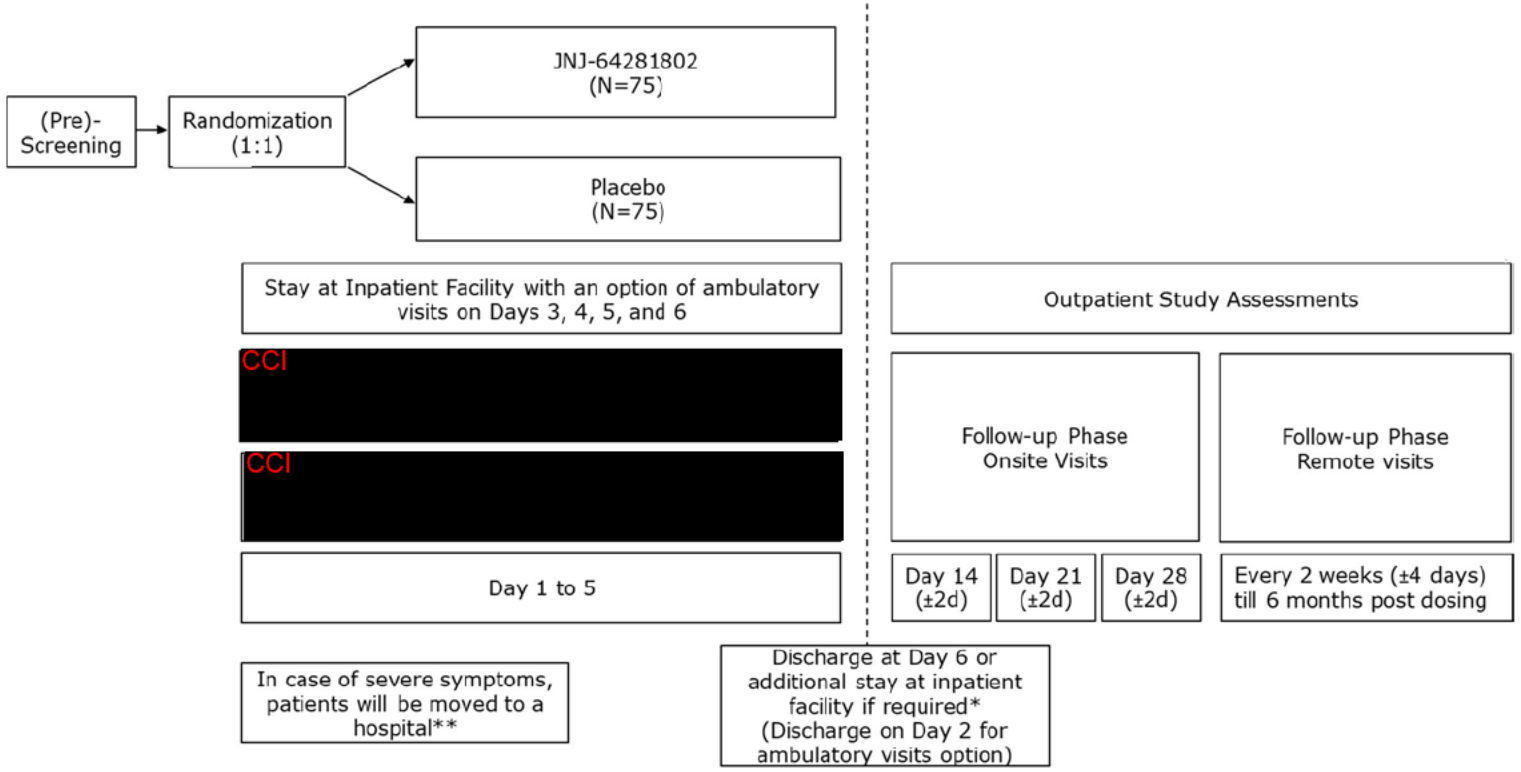
Human Leukocyte Antigen Typing and Pharmacogenomic Analysis: The statistical approach for analysing the exploratory host DNA research may depend on the objective of the analyses (antiviral activity, safety, and PK) and possibly relevant genes at the time of analysis. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented in the clinical study report or a separate report.

INTERIM ANALYSIS:

An interim analysis will be performed when at least 50 participants with a primary dengue infection reached Day 28 or discontinued earlier to check for futility. Conditional power values will be calculated using the observed data and assuming that in the remainder of the trial the effect size used for the sample size calculation will be present. The conditional power provides quantification of the likelihood that the study intervention will ultimately be successful, ie, the probability of claiming a study intervention effect at the completion of the study based on the available interim data. A futility stopping boundary of 25% for the conditional power will be used. This is considered a conservative boundary also reflecting that in this early stage of development it may be best to complete the study to have a larger database to draw conclusions from. In case the probability of a successful trial is lower than the futility boundary, the DRC and study team can take the decision to stop for futility after evaluation of all available data. Assuming the outcome for the primary endpoint as used for the sample size calculations was true, with a treatment effect of 0.30 log10 copies/mL per day DENV RNA clearance on top of placebo, the chance of reaching the futility stopping boundary at the time of the IA is at most 5%. Otherwise, if there is no treatment effect at all, the chance of reaching the futility stopping boundary is at least 60%. The proportion of primary infections will be assessed as well during this interim analysis. If the proportion is lower than expected 60%, the sample size may be increased.

1.2. Schema

Figure 1: Schematic Overview of the Study



Note:
* Participants who develop dengue warning symptoms as defined by the World Health Organization (WHO)[a] will remain at the inpatient facility after Study Day 6 for an additional 3 days.
** Patients with severe dengue (dengue hemorrhagic fever [DHF] or dengue shock syndrome [DSS]), or participants who are hemodynamically unstable or require interventions, can be transferred to a hospital at any time during the inpatient stay, at the investigator's discretion. Participants with severe dengue or dengue warning symptoms after Study Day 9 will be moved to a hospital.
d days

[a] World Health Organization: Dengue. Guidelines for diagnosis, treatment, prevention and control 2009

1.3. Schedule of Activities

Phase	Pre-screening (optional)	Screening/ Baseline[a]	Double-blind Treatment[b]																Follow-Up[b]				Early Exit Visit[b]
			During inpatient stay (or ambulatory visits[y])													Extended stay at inpatient facility (for participants with dengue warning symptoms)			During on Site Visits			Remotely (every 2	
Day		**0**[a]	**1**[a]					**2**					**3**[y]	**4**[y]	**5**[y]	**6**[y]	**7**	**8**	**9**	**14**	**21**	**28**		
Month																							**6**	
CCI																								
Screening/Administrative																								
Pre screening ICF[c]	X																							
Informed consent form (ICF)[d]		X																						
COVID 19 testing[e]		X																						
Demographics		X																						
Medical history and concomitant diseases		X																						
CCI																								
Height		X																						
Body Mass Index (BMI)		X																						
Inclusion/exclusion criteria[f]		X																						
Estimated Creatinine Clearance[g]		X																						
Prestudy therapy		X																						
Serum pregnancy test[h]		X																						

Phase	**Pre-screening** (optional)	**Screening/ Baseline**[a]	**Double-blind Treatment** [b]																				**Follow-Up** [b]				**Early Exit Visit** [b]
			During inpatient stay (or ambulatory visits[y])														**Extended stay at inpatient facility (for participants with dengue warning symptoms)**							**During on Site Visits**			**Remotely (every 2**	
Day		**0** [a]	**1** [a]					**2**					**3**[y]	**4**[y]	**5**[y]	**6**[y]	**7**	**8**	**9**				**14**	**21**	**28**		
Month																										**6**	
CCI [redacted]																											
NS1 rapid test[i]	X	X																									
CCI [redacted]																											
Study Intervention Administration																											
Randomization			❶																								
CCI [redacted]																											
Safety Assessments																											
ECG		X											X			X	X	X	X			X				X
Physical examination[l]		X	X[l]					X[l]					X	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X	X				X
Clinical status			❶																								
Vital signs [m]		X	❶					❶					X	X	X	X	X	X	X	X	X	X				X
Body temperature[n]		X	X					X					X	X	X	X	X	X	X	X	X	X				X

Phase	**Pre-screening** (optional)	**Screening/ Baseline**[a]	**Double-blind Treatment** [b]																			**Follow-Up** [b]				**Early Exit Visit** [b]
			During inpatient stay (or ambulatory visits[y])												**Extended stay at inpatient facility (for participants with dengue warning symptoms)**			**During on Site Visits**			**Remotely (every 2**	
Day		**0** [a]	**1** [a]		**2**			**3**[y]	**4**[y]	**5**[y]	**6**[y]	**7**	**8**	**9**	**14**	**21**	**28**		
Month																		**6**	
CCI [redacted]																			
DENV infection-associated AEs[o]			*~ Continuously ~*																X
DENV infection signs and symptoms checklist			❶		X		X	❶		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																										
Hematology[p] and coagulation[q]		X									X		X	X	X	X[v]	X	X	X	X	X	X		X
Chemistry		X									X		X	X	X	X[v]	X	X	X	X	X	X		X
Pharmacokinetics																										
Blood sample collection for pharmacokinetics (CCI formulation)			❶	X	❶	X	❶	❶	X	❶	X	❶	X	❶	❶	X	X	X	X	X	X	X		X
Blood sample collection for pharmacokinetics (CCI formulation)			❶	X	X	❶		❶	X	X	❶		❶	❶	❶	X	X	X	X	X	X	X		X

Phase	**Pre-screening** (optional)	**Screening/ Baseline**[a]	**Double-blind Treatment** [b]																**Follow-Up** [b]				**Early Exit Visit** [b]
			During inpatient stay (or ambulatory visits[y])													**Extended stay at inpatient facility (for participants with dengue warning symptoms)**			**During on Site Visits**			**Remotely (every 2**	
Day		**0** [a]	**1** [a]					**2**					**3[y]**	**4[y]**	**5[y]**	**6[y]**	**7**	**8**	**9**	**14**	**21**	**28**		
Month																							**6**	
CCI [redacted]																								
Blood sample collection for plasma protein binding[r]			❶										X			X								
Blood sample collection for alpha 1 acid glycoprotein[r]			❶										X			X								
Antiviral activity Assessments																								
Blood sample collection for viral load determination (DENV RNA, infectious virus and NS1)		X				X		❶			X		X	X	X	X	X	X	X	X	X	X		X
Immune/Viral sequencing Assessments																								
Blood sample collection for humoral immunity (IgG, IgM and nAb)		X						❶					X	X	X	X	X	X	X	X	X	X		X

Phase	**Pre-screening** (optional)	**Screening/ Baseline**[a]	**Double-blind Treatment** [b]																		**Follow-Up** [b]				**Early Exit Visit** [b]
			During inpatient stay (or ambulatory visits[y])													**Extended stay at inpatient facility (for participants with dengue warning symptoms)**					**During on Site Visits**			**Remotely (every 2**	
Day		**0** [a]	**1** [a]					**2**					**3**[y]	**4**[y]	**5**[y]	**6**[y]	**7**	**8**	**9**		**14**	**21**	**28**		
Month																								**6**	
CCI [redacted]																									
Blood sample collection for cellular immunity (PBMC)[s]			❶																				X[x]		X
Blood sample collection for viral sequencing		X				X		❶					X	X	X	X	X	X	X		X	X	X		X
Biomarker Assessments																									
Blood sample collection for host RNA		X									X		X	X	X		X	X	X		X	X	X		X
Blood sample collection for serum proteins		X				X		❶					X	X	X	X	X	X	X		X	X	X		X
HLA Typing and Pharmacogenomics (DNA)																									
Blood sample collection[t]			❶																						

Phase	Pre-screening (optional)	Screening/ Baseline[a]	Double-blind Treatment [b]												Follow-Up [b]				Early Exit Visit [b]
			During inpatient stay (or ambulatory visits[y])									Extended stay at inpatient facility (for participants with dengue warning symptoms)			During on Site Visits			Remotely (every 2	
Day		**0** [a]	**1** [a]		**2**		**3[y]**	**4[y]**	**5[y]**	**6[y]**		**7**	**8**	**9**	**14**	**21**	**28**		
Month																		**6**	
CCI [redacted]																			
Ongoing Participant Review																			
Concomitant therapy (including analgesics)			~ *Continuously* ~																X
Adverse events			~ *Continuously* ~																X
Record food and fluid administration			X	X	X	X	X	X	X	X	X	X	X	X											X

❶ predose (within 30 minutes predose), d days, DHS dengue hemorrhagic fever, DSS dengue shock syndrome, ECG electrocardiogram, FSH follicle stimulating hormone, HLA human leukocyte antigen, h hours, ICF informed consent form, NS1 non structural 1 protein, PK pharmacokinetic, m minutes, qRT quantitative reverse transcription.

Footnotes:

a. Screening/baseline assessments start at signing of the ICF. All screening/baseline procedures should take place prior to intake of the first dose of study intervention CCI [redacted] The day of intake of the first dose of study intervention will be considered Day 1.

b. Participants who prematurely discontinue study intervention for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule. Participants who withdraw consent during the treatment or follow-up phase will be offered an optional Early Exit Visit. The optional Early Exit Visit will occur the day of consent withdrawal or as soon as possible thereafter.

c. Participants may initially sign a pre-screening ICF to allow for ambulatory NS1 rapid testing performed by a member of the mobile clinical team as a part of the recruitment strategy.

d. Must be signed before first study-related activity.

e. COVID-19 testing can be performed at the discretion of the investigator, depending on the epidemiological situation.

f. Investigators should ensure that all study enrollment criteria have been met at screening.
g. Calculated by the Modification of Diet in Renal Disease (MDRD) formula.
h. Only for women of childbearing potential. Additional serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.
i. An NS1 rapid test can be performed ambulatory by a mobile clinical team member during pre-screening. Any participant who does not have a documented proof of a positive NS1 test performed by a doctor or by a mobile clinical team member prior to presenting himself/herself at the study site, will undergo an NS1 rapid test at screening.
j. CCI
k.
l. A complete physical examination will be done at screening and at Day 28. At Days 3, 6, 14, and 21, a brief physical examination will be performed. At Days 1, 2, 4, 5, 7, 8, and 9, a physical examination may be performed at the investigator's discretion.
m. Blood pressure, pulse rate, oxygen saturation (spO2) & input-output (I/O) will be measured every 6 hours during inpatient stay and once daily in case of ambulatory visits. Systolic and diastolic blood pressure and pulse/heart rate will be measured supine after at least 5 minutes rest. I/O ratio and spO2 will not be measured at screening.
n. Two-hourly temperature monitoring during inpatient stay, starting at 6 AM in the morning (temperature will not be measured between midnight and 6 AM the next day. In case of ambulatory visits, temperature monitoring will take place once daily.
o. DENV infection associated AEs will be collected as solicited AEs. DENV infection signs and symptoms checklist may be compiled by any delegated study team member, and it may be used to assist in the collection of DENV infection associated AEs.
p. Any participant who has a hematocrit rise with values >20% of the baseline at any timepoint will require full blood count (FBC) monitoring every 4 hours (at the discretion of the investigator).
q. Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT) will be used to determine the effect of JNJ 64281802 treatment on blood coagulation during the treatment and on-site follow-up periods.
r. Plasma protein binding and alfa-1-acid glycoprotein will be determined in a subset of 20 participants.
s. Peripheral blood mononuclear cell (PBMC) samples may be analyzed in a subset of participants to assess DENV-specific T and B cell immune responses.
t. The pharmacogenomic (DNA) sample should be collected at the specified time point, however, if necessary, it may be collected at a later time point without constituting a protocol deviation.
u. After the last on-site visit at Day 28, participants will be followed up remotely (eg, phone call, text message) until 6 months after the first dosing day. During this every-2-weeks contact, they will be inquired for any dengue-related signs and symptoms.
v. At Day 6, safety laboratory testing can be performed at the discretion of the investigator.
w. CCI
x. At Day 28, the volume of blood samples for PBMC isolation can be reduced from 30 mL to 10 mL, subject to the local regulations and investigator's request.
y. Optional ambulatory visits on Days 3, 4, 5, and 6 at the investigator's discretion.

2. INTRODUCTION

Dengue is caused by any of the four antigenically distinct DENV serotypes (DENV -1, -2, -3, and -4), which belong to the genus *Flavivirus* in the family of the *Flaviviridae*. The DENV is a human pathogen transmitted through the bite of an infected female mosquito of the genus *Aedes*, mainly of the species *Aedes aegypti* and to a lesser extent *Aedes albopictus*.[0] After near-extinction in the early 1970s, dengue has spread to more than 125 countries, and has again become endemic in the United States of America and its territories.[0] About half of the global population is currently at risk of becoming infected with DENV, ranking dengue among the top 10 threats to global health in 2019.[0,0,0,0]

Dengue is widespread throughout the tropics, with local variations in risk influenced by rainfall, temperature, and rapid urbanization. The exponential growth of the number of dengue cases reflects the global spread of the mosquito vectors, which is driven by climate changes and, more importantly, human population growth, urbanization, and globalization. It is anticipated that epidemic dengue will continue to increase in magnitude and frequency, as the main drivers of DENV spread are projected to intensify.[0] Major dengue outbreaks in many countries have burdened health care systems, especially in resource-limited countries. Consequently, dengue is considered a global health concern.

The actual numbers of dengue cases are underreported, and many cases are misclassified as other febrile illnesses such as malaria. It is estimated that there are 390 million DENV infections globally per year of which 96 million infections manifest clinically (with any severity of the disease).[0] On average, each year about 500,000 dengue cases require hospitalization due to severe and life-threatening disease and up to 25,000 patients die due to dengue.[0] There is, therefore, a need to develop an anti-DENV molecule for the prevention and treatment of dengue.

During a primary DENV infection, 75% of the individuals remain asymptomatic.[0] Those that show clinical symptoms, mainly develop an acute, self-limiting febrile illness. The first clinical symptoms occur 3 to 8 days after a bite by a DENV infected and viremic mosquito. Resolution of symptoms usually occurs within 4 to 7 days due to a robust innate and adaptive immune response.[0] A smaller percentage of DENV infections result in severe dengue outcomes such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Secondary DENV infections or infections with particularly virulent viral strains are thought to be associated with an increased risk for severe dengue.[0]

During classical dengue fever, an abrupt onset of fever is accompanied by a wide range of potential symptoms, ie, myalgia, arthralgia, headache, and rash; with retro-orbital pain and lower back pain being prototypical symptoms. Also vomiting, nausea, and anorexia are common.[0] The critical phase is characterized by an increased propensity for capillary leakage and hemorrhage, typically manifested by petechiae, hematuria, and gastrointestinal hemorrhage.[0,0] Without early diagnosis and proper management, some patients experience shock from blood loss or plasma leakage, which can result in a sudden deterioration of the patient's condition. [0]

An issue of particular importance to dengue is a process called antibody-dependent enhancement. Briefly, when a person is infected for the first time with a DENV serotype (eg, serotype 1), a serotype-specific antibody response is generated. These antibodies bind to the dengue serotype 1 virus specifically and cover the virus completely. As a result, these antibody-covered virus complexes are taken up by macrophages. Consequently, these complexes undergo endocytosis and the dengue virus is destroyed. However, the risk of developing DHF/DSS is especially increased after secondary dengue infection with a different serotype than that of the primary infection. The non-neutralizing, cross-reactive antibodies generated during the primary infection (in this example against DENV-1), partially interact with and cover the virus of the different serotypes. Consequently, these partially antibody coated virus complexes are now able to escape the endocytic pathway, enabling them to replicate in these immune cells.[0] Overall, this leads to a higher number of infected target cells, a higher viral load, and a higher probability to develop DHF/DSS. Antibody-dependent enhancement reinforces the critical need to develop a small molecule which has antiviral activity against all four serotypes of DENV.

JNJ-64281802 is a novel anti-dengue small-molecule targeting DENV non-structural protein (NS)4B. It has shown potent antiviral activity across all 4 DENV serotypes in preclinical studies.[0] A Phase 1 first-in-human study 64281802DNG1001 (further referred to as DNG1001) to assess the safety, tolerability, and pharmacokinetics (PK) of increasing single and multiple oral doses of JNJ-64281802 in healthy adult participants has been performed. JNJ-64281802 is currently being evaluated for the prevention and treatment of dengue infection.

This is a Phase 2a, multicenter study to be conducted in Singapore and Vietnam. The aim of the study is to examine the antiviral activity, safety and tolerability, and PK of JNJ-64281802, compared to placebo, and to evaluate the improvement in clinical signs and symptoms with the administration of JNJ-64281802 for the treatment of dengue. For the most comprehensive nonclinical and clinical information regarding JNJ-64281802, refer to the latest version of the Investigator's Brochure (IB) and Addenda for JNJ-64281802.[0,0]

The term “study intervention” throughout the protocol, refers to JNJ-64281802.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Currently, there is no dengue-specific treatment available and thus, clinical treatment is principally supportive in nature.

In December 2015, the first vaccine against DENV was licensed in Mexico. The chimeric yellow fever DENV tetravalent dengue vaccine (CYD-TDV; Dengvaxia®) is a live attenuated vaccine developed by Sanofi Pasteur. By November 2016, the vaccine had been approved for use in 18 countries including Brazil, Mexico, El Salvador, Costa Rica, and the Philippines. In late 2017, the vaccine was withdrawn again from the Philippine market because of safety concerns, which

led to revocation of the vaccine's licensure in the Philippines in February 2019. In May 2019, the vaccine was approved in the USA for the prevention of dengue disease caused by all DENV serotypes (DENV-1, -2, -3, and -4) in individuals, 9 through 16 years of age, who have laboratory confirmed previous dengue infection and who live in endemic areas. The widespread use of the vaccine, however, is not foreseen per the World Health Organization (WHO) working group for immunization, as a number of factors need further consideration. The Strategic Advisory Group of Experts recommended countries to consider the introduction of Dengvaxia® only in geographic settings (national or subnational) with high dengue endemicity. According to the National Environment Agency, Singapore had reported a total of 14,328 cases of dengue fever as of November 2019, representing the highest number of dengue cases since the year 2016. In addition, new cases continue to be reported every week, with 20,600 cases being reported by July 27 of 2020[0]. Dengue virus infection is endemic in Vietnam with an estimated burden of about 2 million yearly infections,[0,0] with high rates of secondary infections with the DENV1 and DENV2 serotypes[0]. However, the official average number reported by the Ministry of Health is approximately 95,000 cases per year over the period 2002 to 2020. This under-reporting may be due to 2 main factors: (i) dengue surveillance in Vietnam is mostly passive, relying on clinical cases reported by patients seeking healthcare[0] and (ii) up to 80% of the cases may be asymptomatic or minimally symptomatic and will likely not seek healthcare[0]. With the limited prophylactic options based on one approved vaccine and the fact that there is no dengue-specific treatment available, the present study will look into the antiviral activity of JNJ-64281802 in participants with primary DENV infection.

Considering the higher DENV RNA viral load values and the lower variability between these values in patients with a primary DENV infection when compared to patients with a secondary DENV infection, the primary objective of the current study is restricted to the evaluation of the antiviral activity of JNJ-64281802 in participants with a primary DENV infection.

2.2. Background

Nonclinical Studies

In vitro Pharmacology

The anti-DENV-2 activity (50% effective concentration [EC_{50}]) of JNJ-64281802 was tested in vitro in Vero cells infected with DENV-2/16681, which was labeled with enhanced green fluorescent protein (eGFP). JNJ-64281802 exhibited a median 50% effective concentration (EC50) of 0.05 nM with a selectivity index of 48,000 against dengue virus (DENV) 2/16681/enhanced green fluorescent protein (eGFP) in Vero cells. In the presence of 50% human serum, the antiviral activity of JNJ-64281802 against DENV 2/16681/eGFP decreased 28-fold.

The antiviral activity of JNJ-64281802 was tested using reverse transcription quantitative polymerase chain reaction (RT-PCR) against a panel of DENV strains belonging to the 4 major serotypes, including lab-adapted strains and clinical isolates obtained from several sources. JNJ-64281802 exhibited potent antiviral activity against all 4 DENV serotypes (lab-adapted strains and clinical isolates) with subnanomolar or low nanomolar median EC_{50} values against most strains, and a high specificity towards DENV.

In vivo Pharmacology

In DENV-2 inoculated mice treated with JNJ-64281802, dose-dependent viral ribonucleic acid (RNA) reductions in serum and tissues (spleen, kidney, and liver) compared with vehicle treated mice were observed and were linked with a significant effect on survival.

In a non-human primate model, no viral RNA was detected for the highest doses of JNJ-64281802 (0.93 and 3 mg/kg/dose) against DENV-2/16681 and for the dose of 6 mg/kg against DENV-1/45AZ5 given prophylactically, indicating that JNJ-64281802 is highly effective in preventing infection after DENV challenge in this rhesus monkey model.

Safety Pharmacology

Cardiovascular function was not affected in dogs up to 600 mg/kg (maximum plasma concentration [C_{max}] 7,340 ng/mL). In rats, respiratory function was not affected up to 1,000 mg/kg and neurofunctional testing up to 1,000 mg/kg (C_{max} 9,870 ng/mL) did not lead to major effects.

Pharmacokinetics and Metabolism

In vitro Permeability: JNJ-64281802 demonstrated low in vitro permeability in LLC-PK1 cells stably transfected with multidrug resistance protein 1 (MDR1) and is likely a P-glycoprotein substrate.

Absorption: JNJ-64281802 was generally slowly absorbed with moderate oral bioavailability across species (absolute bioavailability: 25%-66%). In fasted male dogs, the highest JNJ-64281802 exposure values (C_{max} and area under the plasma concentration-time curve from 0 hours to infinity [AUC0-∞]) were obtained with a CCI (Gelure 44/14) (1.2-fold) compared with a 100% PEG400 CCI. After repeated oral dosing of JNJ-64281802 in rats and dogs, exposure increased less than dose proportionally, and was higher than after single dosing.

Distribution: In vitro plasma protein binding of JNJ-64281802 was high across nonclinical species and humans, with an unbound percentage ranging from 0.00472% in mice to 0.0339% in guinea pigs, and 0.00621% in humans. In rats, distribution was wide throughout the body with highest levels in liver.

Metabolism: Predominant routes of metabolism were through demethylation and oxidation via cytochrome P450 (CYP)3A4 and possibly CYP2C19, subsequently glucuronidation as well as direct N-glucuronidation via uridine diphosphate-glucuronosyltransferase (UGT)1A9 and possibly UGT1A4, UGT1A8, and UGT1A10. There was no indication for reactive metabolite formation.

Elimination: In rats, elimination of JNJ-64281802 was almost completely via metabolism with low/negligible excretion in bile (approximately 3%) and urine (<0.001%).

Pharmacokinetic drug-interaction: In vitro, JNJ-64281802 did not induce CYP1A2 at 1 and 10 µM, nor CYP3A4 at 1 µM. At 10 µM, JNJ-64281802 was shown to be a CYP3A4 inducer. JNJ-64281802 showed weak inhibition potential towards CYP1A2 and CYP2D6 (50% inhibitory concentration [IC50] >30 µM), and inhibition of CYP2C9 (IC50 3.7 µM), CYP2C8

(IC50 7.4 µM), and CYP2C19 (IC50 10.3 µM). Due to metabolic activation of CYP3A4/5-mediated metabolism of midazolam and CYP3A4-mediated metabolism of testosterone, no results were available for these CYP/probe substrate combinations, and time-dependent inhibition potential could not be assessed.

Toxicology

In rats, the NOAEL after 31 days was 1,000 mg/kg/day (area under the plasma concentration-time curve from 0 to 24 hours [$AUC_{0\ 24h}$] 524,000 and 706,000 ng.h/mL in male and female rats, respectively). Minor reduction in food consumption and minor, nonadverse changes in clinical pathology parameters were observed. Findings in liver (hypertrophy), lungs (foci, macrophage aggregates), thyroid gland (follicular cell hypertrophy), mammary gland (atrophy), adrenal gland (hypertrophy), and thymus (lymphocytic apoptosis) were fully reversible. There were no apparent functional changes to these organs.

In dogs, the NOAEL after 31 days was 200 mg/kg/day ($AUC_{0\ 24h}$ 129,000 and 177,000 ng.h/mL in male and female dogs, respectively). Minimal effects on body weight gain (female dogs) and on some serum parameters were observed. Dosing at 400 mg/kg twice daily (800 mg/kg/day) led to individual body weight loss and high liver enzyme increases. Good reversibility was observed.

JNJ-64281802 was not considered genotoxic or phototoxic, and there were no test article-related effects on embryo-fetal development in pregnant rats and rabbits. JNJ-64281802 is considered unlikely to be a primary mitochondrial toxicant under the conditions of an in vitro mitochondrial toxicity assay.

Clinical Studies

Up to the cutoff date of 10 September 2021, a total of 223 healthy adult participants received JNJ-64281802 and 19 healthy adult participants received placebo.

One Phase 1 study (64281802DNG1001) has been completed. Four Phase 1 studies (64281802DNG1004, 64281802DNG1005, 64281802DNG1006, and 64281802DNG1008) are currently ongoing. Two Phase 2 studies (64281802DNG2001 and 64281802DNG2002) are currently ongoing.

64281802DNG1001

The Phase 1 study (64281802DNG1001) has been completed: a total of 122 healthy adult participants received either JNJ-64281802 (103 participants) or matching placebo (19 participants).

The Phase 1, double-blind, randomized, placebo-controlled, first-in-human study 64281802DNG1001 (EudraCT number: 2018-002201-62), further referred to as DNG1001examined the safety, tolerability, and PK of increasing single and multiple oral doses of JNJ-64281802 in healthy adult participants. An open-label, randomized, crossover, relative oral bioavailability part was included to study the PK and safety following CCI formulation concepts compared with CCI, and to study the food effect on JNJ-64281802.

Safety

JNJ-64281802 was generally safe and well tolerated. No safety concerns were identified at single doses up to 1,200 mg and at multiple doses up to 560 mg once daily for 10 days or 400 mg once daily for 31 days. Two Grade 2 events of rash occurred in the multiple ascending dose part that were considered very likely related to JNJ-64281802 by the investigator. One Grade 2 rash occurred in a participant in the 10-day 560 mg JNJ-64281802 group on the last day of dosing (Day 10) and resolved after 35 days. The other Grade 2 rash occurred in a participant in the 31-day 400 mg JNJ-64281802 group on dosing Day 13 and resolved after 47 days. This participant completed the 31-day dosing period as planned.

Exposure-response analysis based on time-matched QT interval corrected for heart rate (QTc) Holter data supports that within the investigated concentration range of study 64281802DNG1001. There is no evidence of an effect of JNJ-64281802 on cardiac repolarization.

Human Pharmacokinetics

Following single-dose administration with JNJ-64281802 (50-1,200 mg), formulated as CCI [redacted], the exposure increased dose proportionally from 50 to 150 mg and less than dose proportionally from 240 to 1,200 mg, while following multiple dosing the exposure of JNJ-64281802 increased closer to dose proportionally over the investigated dose range (50-560 mg) compared with single dosing.

The median time to maximum concentration (t_{max}) ranged from 7 to 10 hours, and the $t_{1/2}$ was 6.3 to 9.2 days following single and multiple dosing. The accumulation factor varied from 4.3 to 7.3 following 10 days of daily dosing and was 14.6 following 31 days of daily dosing. The intersubject variability in exposure, expressed as percentage coefficient of variation (CV), was 8.6% to 58%.

A single dose of the active pharmaceutical ingredient blend in CCI [redacted] (200 mg, fasted) compared with a single dose of CCI [redacted] (200 mg, fasted) showed a geometric mean ratio (90% confidence interval [CI]) between 20.6% (16.2%-26.3%) and 22.1% (17.2%-28.5%). A single dose of the CCI [redacted] (2x100 mg, fasted) compared with a single dose of CCI [redacted] (200 mg, fasted) showed a geometric mean ratio (90% CI) between 81.6% (65.2%-102.1%) and 85.9% (67.1%-109.9%). An approximately 3-fold increase in exposure was observed when the active pharmaceutical ingredient blend in CCI [redacted] was administered with a high-fat, high-calorie breakfast compared with fasted conditions, without a relevant difference in t_{max} or apparent $t_{1/2}$.

The food effect following administration of CCI [redacted] was not investigated in the oral bioavailability part of study DNG1001. CCI [redacted]

64281802DNG1006

In Part 1 of study 64281802DNG1006, further referred to as DNG1006, the relative oral bioavailability of JNJ-64281802 in healthy participants was assessed when administered as

CCI formulation concepts compared with CCI, following a single oral dose in fasted conditions. CCI

CCI When administered with a standardized breakfast, JNJ-64281802 C_{max} was increased by 33%, 76%, and 178% compared to fasted conditions for a single dose of 50 mg, 200 mg, and 800 mg, respectively. For AUC_{∞}, this increase was 12%, 76%, and 143%, respectively.

64281802DNG1005

In study 64281802DNG1005, the potential for drug-drug interactions (DDIs) was assessed when administering a single dose of 200 mg JNJ-64281802 concomitantly with 200 mg itraconazole once daily, a strong CYP3A4 and P-glycoprotein inhibitor. Coadministration with itraconazole significantly increased the plasma exposure of JNJ-64281802 over the full profile, by 1.87-fold for $AUC_{0\infty}$ compared with single administration of JNJ-64281802 alone. A slight increase of 1.12-fold for C_{max} was also observed. The coadministration with itraconazole increased plasma exposure (AUC_{504h}) of JNJ-64281802 over 504 hours by 1.53-fold.

64281802DNG1004

In part 1 of study 64281802DNG1004, the potential for DDIs was assessed when administering a single dose of a drug cocktail including caffeine, warfarin (supplemented with vitamin K), omeprazole, dextromethorphan, midazolam, repaglinide and rosuvastatin concomitantly with both a single dose and/or multiple doses of JNJ-64281802. Exposure to caffeine (CYP1A2 substrate) was increased by 12%, warfarin (CYP2C9 substrate) by 40%, omeprazole (CYP2C19 substrate) by 36% while dextromethorphan exposure was decreased by 12%, midazolam (CYP3A4 substrate) was increased by 59%, repaglinide (CYP2C8 substrate) by 58%, and rosuvastatin (BCRP substrate) by 182%. This indicates that JNJ-64281802 is a moderate inhibitor of BCRP, and a weak inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2C19.

For the most comprehensive nonclinical and clinical information regarding JNJ-64281802, refer to the latest version of the IB and Addenda for JNJ-64281802.[0,0]

Benefit-Risk Assessment

Below, the known and potential benefits and risks of JNJ-64281802 are discussed. More detailed information about the known and expected benefits and risks of JNJ-64281802 may be found in the IB for JNJ-64281802.

2.3.1. Known Benefits

The clinical benefits of JNJ-64281802 remain to be established.

2.3.2. Potential Benefits

Results from this study may be useful to support the antiviral development program for JNJ-64281802, and thereby contribute to the development of a new anti-DENV compound for treatment of patients with dengue infection.

2.3.3. Known Risks

All therapies have the potential to cause adverse experiences. To date, limited clinical data with JNJ-64281802 are available from the Phase 1 first-in-human study DNG1001 in healthy adult participants (Section 2.2). JNJ-64281802 was generally well tolerated, and no safety concerns were identified at single doses up to 1,200 mg and at multiple doses up to 560 mg once daily for 10 days or 400 mg once daily for 31 days.

2.3.4. Potential Risks

Reproductive Risks and Pregnancy

Animal studies with JNJ-64281802 did not indicate harmful effects with respect to reproductive toxicity. There were no test article-related effects on embryo-fetal development in pregnant rats up to 500 mg/kg/day and in pregnant rabbits up to 180 mg/kg/day, which were the highest dose levels tested. Excessive maternal toxicity was evident at 180 mg/kg/day in rabbits.

The effect of JNJ-64281802 on sperm, on conception, or on a fetus or nursing baby is unknown. In addition, no drug-drug interaction studies have been performed and hence the potential effect of JNJ-64281802 on contraceptive efficacy of hormonal contraceptives is unknown. Therefore, the following should be adhered to:

- Women who are pregnant, breastfeeding, or planning to become pregnant during the study or within 90 days after last dose of study drug cannot receive study drug. A woman must be not of childbearing potential, or of childbearing potential and practicing a highly effective, preferably user-independent method of contraception (refer to Section 10.5, Appendix 5 for examples) and agrees to remain on a highly effective method while receiving study drug and until 90 days after last dose the end of relevant systemic exposure. Use of highly effective methods of contraception should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. A woman using oral contraceptives should use an additional barrier-based contraceptive method (on top of what is required per Inclusion Criterion 10 in Section 5.1).
- All women of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin) pregnancy test at screening. Additional serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.
- A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for up to 90 days after last dose of study drug.
- A male participant must wear a condom during the study and for up to 90 days after last dose of study drug when engaging in any activity that allows for passage of ejaculate to another

person. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condoms may break or leak.

- A male participant must agree not to donate sperm for the purpose of reproduction during the study and for up to 90 days after last dose of study drug.

Potential Genotoxicity

JNJ-64281802 was not genotoxic when tested in the Ames assay and in the in vitro and in vivo micronucleus assays.

Carcinogenicity and Impairment of Fertility

No carcinogenicity or fertility studies have been performed.

Risks From Blood Draws

Blood drawing may cause pain/tenderness, bruising, bleeding, lightheadedness, dizziness, vasovagal response, syncopal episodes, and, rarely, infection at the site where the blood is taken.

Concomitant Vaccination

Concomitant vaccination might have an influence on both safety profile and immunogenicity of JNJ-64281802. Likewise, JNJ-64281802 might have an influence on both safety profile and immunogenicity of any concomitant vaccination. As a result, vaccinations are not allowed until 30 days after the last dose of study drug. Participants will be allowed to receive an authorized/licensed COVID-19 vaccine at any time before, during, and after the study (see Section 10.9, Appendix 9: Guidance on Study Conduct During the COVID-19 Pandemic).

Rash

In study DNG1001, 2 Grade 2 events of rash occurred in the multiple ascending dose part (N 47) that were considered very likely related to JNJ-64281802 by the investigator. Both events were resolved after 35 to 47 days. If in study DNG2003, a causal relationship between the events of rash and the study drug cannot be excluded, additional safety follow-up procedures will apply, as described in the rash management protocol in Section 10.7, Appendix 7.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with JNJ-64281802 are justified by the anticipated benefits that may be afforded to participants with confirmed dengue fever.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Investigate the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV RNA in primary DENV infection	• Area under the log_{10}-transformed DENV RNA viral load (log_{10} VL) curve from baseline until Day 5 ($AUC_{D1\text{-}D5}$ [log_{10}VL]).

Objectives	Endpoints
Secondary	
• Assess the safety and tolerability of JNJ-64281802 in primary and secondary DENV infection	• AEs • ECGs • physical examinations • vital signs • clinical laboratory assessments
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on other virological endpoints in primary DENV infection	• Virologic endpoints derived from the DENV RNA, including Occurrence of detectable DENV RNA at each time point in primary DENV infection Time to undetectable DENV RNA in primary DENV infection
• Evaluate the PK of JNJ-64281802	• PK parameters for JNJ-64281802
Exploratory	
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on DENV infectious viral titer (further referred to as viremia) in primary DENV infection	• Virologic endpoints derived from viremia, including Area under the log_{10}-transformed viremia curve from baseline until Day 5 in primary DENV infection Occurrence of detectable viremia at each timepoint in primary DENV infection Time to undetectable viremia in primary DENV infection
• To explore the relationship between the exposure and antiviral activity of JNJ-64281802	• PK (plasma concentrations or exposure parameters) of JNJ-64281802. • Area under the log10-transformed viremia or DENV RNA viral load.
• Investigate the antiviral activity of JN-64281802 versus placebo in terms of reduction of DENV RNA in secondary DENV infections and in all DENV infections	• Virologic endpoints derived from the DENV RNA, viral load, including Area under the log_{10}-transformed DENV RNA viral load curve from baseline until Day 5, in secondary DENV infection Occurrence of detectable DENV RNA at each time point in secondary DENV infection Time to undetectable DENV RNA in secondary DENV infection

Objectives	Endpoints
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on viremia in secondary DENV infections and in all DENV infections	• Virologic endpoints derived from viremia, including Area under the log_{10}-transformed viremia curve from baseline until Day 5 in secondary DENV infection Occurrence of detectable viremia at each timepoint in secondary DENV infection Time to undetectable viremia in secondary DENV infection
• Investigate the effect of JNJ-64281802 versus placebo on the change in hematology values over time (leucocytes, platelets and hematocrit)	• The maximal decrease from baseline (per participant) observed in platelet counts from Day 2 to Day 5 • The maximal decrease from baseline (per participant) observed in leucocyte counts from Day 2 to Day 5 • The maximal increase from baseline (per participant) observed in hematocrit concentration from Day 2 to Day 5
• Investigate the effect of JNJ-64281802 versus placebo on the immunological profile	• The occurrence and magnitude of anti-DENV total IgM and IgG antibody titers
• To explore the effect of JNJ-64281802 versus placebo on DENV-related clinical signs and symptoms	• Time to resolution of dengue signs and symptoms • Severity of dengue signs and symptoms
• To assess changes in the viral genome sequence (with a focus on NS4B) in participants with detectable DENV RNA	• Changes in the viral genome sequence at and between first viral isolation and last viral isolation
• To explore the DENV NS1 serum protein levels	• Occurrence and magnitude of DENV NS1 serum protein levels
• To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802	• HLA genotyping and pharmacogenomic analyses
The following additional exploratory objectives may be evaluated at the discretion of the sponsor: • Investigate the effect of JNJ-64281802 versus placebo on immunological profile based on occurrence and magnitude of anti-DENV cellular immune responses • To explore changes in serum protein levels (including cytokines) • To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802 based on biomarker analysis via transcriptional profiling of host RNA • The occurrence and magnitude of an anti-DENV neutralizing antibody response	

Abbreviation key: AE(s) adverse event(s), AUC area under the curve, DENV dengue virus, ECG: electrocardiogram, HLA human leukocyte antigen, Ig Immunoglobulin, NS non structural, PK pharmacokinetic, RNA ribonucleic acid, VL viral load

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to reduction in viral load in participants with a primary DENV infection, as measured by area under the log_{10}-transformed DENV RNA viral load curve from baseline until Day 5.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2a interventional study in participants aged ≥18 or ≥21 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤60 years. Participants who report with an onset of fever of <48-hour duration at screening, and who test positive for DENV infection by the NS1 assay will be randomized into the study. Randomization will be stratified by country and by duration of dengue symptoms from onset until the time of randomization (≤24 hours and >24 hours).

The population will include participants with a primary and a non-primary or secondary infection. The difference between the 2 subpopulations will be determined before data base lock and will be based on the IgG profile.

A planned target of 150 male and female participants will be randomly assigned in a ratio of 1:1 to receive JNJ-64281802 or placebo in this study with approximately 75 participants planned per intervention group. The sample size can be revised after an interim analysis on the proportion of primary versus secondary DENV infections (refer to Section 9.5, Interim Analysis).

There are three sequential phases in the study: screening/baseline, double-blind treatment and follow-up. Study participants will complete the screening/baseline visit on Day 0 (predose), followed by a double-blind treatment phase from Day 1 to Day 6 or Day 9 (for participants with dengue warning symptoms). During the double-blind treatment phase, the participants will be admitted to an inpatient facility. At the investigator's discretion, ambulatory visits instead of inpatient treatment can be allowed at Days 3, 4, 5, and 6. All participants will be followed up for a total of 6 months after the first dosing day. The entire study duration for each participant will be approximately 6 months (±4 days). The participants will complete the study after having completed the final remote follow-up assessment planned 6 months (±4 days) after having received the first dose of study intervention, unless ongoing adverse events (AEs) require monitoring.

Mobile clinical teams consisting of trained and delegated site staff (eg, nurses, clinical research coordinators [CRCs]) will visit the clinics and communities to sensitize and pre-screen potential study participants and will play an active role in participant recruitment. Individuals with a suspected DENV infection will be asked to undergo an NS1 rapid test after signing a pre-screening ICF during an ambulatory visit at a health care facility organized by the mobile clinical teams.

The study sites will be open to receive referrals of participants who have consulted a health care facility (eg, clinic/polyclinic, hospital) or practitioner (eg, general practitioner [GP], medical

doctor [MD], nurse) with an onset of fever within the last 48 hours, as reported by the participant, and who tested positive for DENV infection by the NS1 assay at the health care facility. Individuals who test positive during an ambulatory visit or as part of Standard of Care DENV NS1 rapid testing, will be referred to the study site to further coordinate informed consent signing and completion of eligibility assessments. In addition, participants may also report directly to the study site. Participants identified at the study site with an onset of fever as reported by the participant within the last 48 hours, and who test positive for DENV infection by the NS1 assay performed at the site after signing the ICF, will undergo eligibility assessments.

The screening/baseline assessments are to be completed as quickly as possible at the study site. Participants who successfully meet all inclusion criteria and none of the exclusion criteria, will be enrolled and admitted to an inpatient facility. The participants will then be randomized to receive placebo or JNJ-64281802. CCI [redacted] Results of screening assessments need to be documented in the electronic case report form (eCRF).

Placebo or JNJ-64281802 will be administered on Days 1 to 5, starting from the day of randomization (Day 1). The participants will stay at the inpatient facility from Day 1 to Day 6 (with an option to attend ambulatory visits on Days 3, 4, 5, and 6 instead at the investigator's discretion) and daily clinical monitoring will be conducted, and blood samples will be collected as shown in Schedule of Activities. Oral intake of food and fluids will be recorded on Days 1, 2, 3, 4, and 5 of dosing.

JNJ-64281802 (in either CCI [redacted] formulation) or matching placebo will be administered according to the following dosing regimens:

CCI [redacted]

The CCI [redacted] formulation will be introduced for use in newly recruited participants, when it becomes locally available.

CCI [redacted]

CCI [redacted]

When dosed in fasted condition in 16 healthy volunteers, the JNJ-64281802 C_{max} and AUC_{∞} were similar between CCI [redacted] and CCI [redacted], with geometric mean ratios of 1.06 and 1.00, respectively. CCI [redacted] When administered with a standardized breakfast, JNJ-64281802 C_{max} was increased by 33, 76, and 178% compared to fasted conditions for a single dose of 50, 200 and 800 mg, respectively. For AUC_{∞} this increase was 12, 69, and 143%, respectively.

CCI [redacted]

The participants will be discharged from the inpatient facility on Day 6 (on Day for ambulatory visits) after the assessments indicated in the Schedule of Activities have taken place and given their clinical status is satisfactory for discharge in the opinion of the investigator. Participants who develop dengue warning symptoms as defined by WHO[0] will remain at the inpatient facility after Study Day 6 for an additional 3 days and planned outpatient assessments will be performed by the study team members, where required. Patients with severe dengue (DHF or DSS), or participants who are hemodynamically unstable or require interventions, can be transferred to a hospital at any time during the inpatient stay, at the investigator's discretion. Participants with severe dengue or dengue warning symptoms after Study Day 9 will be moved to a hospital. After discharge, the participants will be asked to return on Days 14, 21, and 28 (±2 days) and, thereafter, to perform remote follow-up visits every two weeks (±4 days) till 6 months post dosing for assessments specified in the Schedule of Activities. If the participant remains in the inpatient facility beyond Day 6, planned outpatient study assessments will be performed at the inpatient facility as specified in the Schedule of Activities.

At time points specified in the Schedule of Activities, key assessments during the study will include the antiviral activity (as measured by DENV RNA viral load, viremia, and NS1), safety and tolerability, and PK of JNJ-64281802. Safety and tolerability will be assessed through AE reporting, physical examinations, vital signs, ECG and clinical laboratory tests. Furthermore, the effect of JNJ-64281802 on the clinical course of DENV infection will be explored based on the investigator's assessment of DENV infection-associated AEs. In addition, the study also includes the collection of blood samples for PK analysis, viral genome sequencing, pharmacogenomic (DNA) research, cellular immune response analysis, and exploratory biomarker analyses, including serum protein measurements and transcriptional profiling of host RNA.

Participants who prematurely discontinue study intervention for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule. Participants who withdraw consent during the treatment or follow-up phase will be offered an optional Early Exit Visit. The optional Early Exit Visit will occur the day of consent withdrawal or as soon as possible thereafter.

An Internal Data Review Committee (DRC) will be commissioned for this study. The members of DRC will consist of a Global Medical Safety (GMS) therapeutic area safety head, a clinician, a clinical pharmacologist, a virologist, and a statistician, none of whom will be part of the study team or involved in the conduct of the study. Any deaths related to dengue, admission to the intensive care unit or severe dengue (DHF/DSS) will trigger a safety data review by the DRC. If, in the judgment of the investigator and/or the sponsor's study-responsible physician, a significant or unexpected safety event occurs, the DRC will review unblinded safety data. Quarterly (every 3 months or when 50 participants are enrolled, whichever comes first), a DRC safety analysis where DRC members review unblinded data, will take place. The DRC responsibilities, authorities, and procedures will be documented in its charter. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

The primary analysis will be performed when all participants reached Day 28 or discontinued earlier. The final analysis will be performed when all participants completed the study or discontinued earlier.

An interim analysis will be performed when at least 50 participants with a primary dengue infection reached Day 28 or discontinued earlier to check for futility or superiority. To check for futility, conditional power values will be calculated using the observed data and assuming that in the remainder of the trial the effect size used for the sample size calculation will be present. The conditional power provides quantification of the likelihood that the study intervention will ultimately be successful, ie, the probability of claiming a study intervention effect at the completion of the study based on the available interim data. A futility stopping boundary of 25% for the conditional power will be used. This is considered a conservative boundary also reflecting that in this early stage of development it may be best to complete the study to have a larger database to draw conclusions from. In case the probability of a successful trial is lower than the futility boundary, the DRC and study team can take the decision to stop for futility after the evaluation of all available data. If early superiority on the primary endpoint can be established, the DRC and study team can take the decision to open the study for participants at risk of severe dengue. Assuming the outcome for the primary endpoint as used for the sample size calculations was true, with a treatment effect of 0.30 log10 copies/mL per day DENV RNA clearance on top of placebo, the chance of reaching the futility stopping boundary at the time of the IA is at most 5%. Otherwise, if there is no treatment effect at all, the chance of reaching the futility stopping boundary is at least 60%. As the study will proceed even if superiority is achieved, no correction for multiple testing will be done.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are

evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to determine the human leukocyte antigen (HLA) type of each participant and to allow the identification of genetic factors that may influence the PK, antiviral activity, or safety/tolerability of JNJ-64281802. A blood sample for HLA genotyping and for pharmacogenomic research will be collected, preferably at baseline (ie, before first dose of study drug). Participation in the HLA genotyping and pharmacogenomic research is mandatory.

Biomarker samples will be collected to evaluate the mechanism of action of JNJ-64281802 or to help explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802 and aid in evaluating the drug-clinical response relationship. Samples can only be used for research related to JNJ-64281802 or DENV infection or may be used to develop tests/assays related to JNJ-64281802 or DENV infection.

DNA and Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

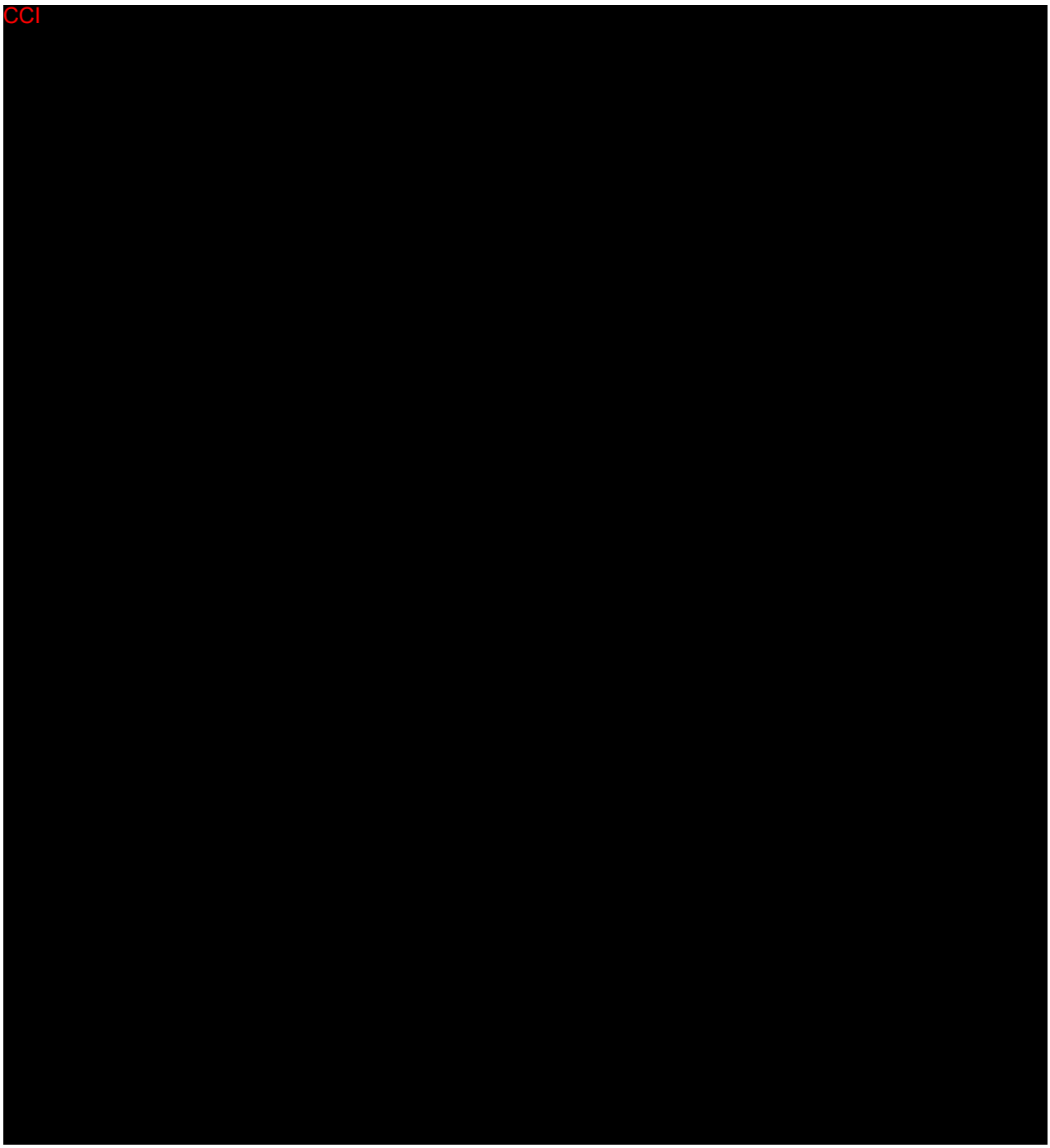
When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the adolescent with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. For the purposes of this study, all references to participants who have provided consent refers to the participants and his or her parent(s) or the participant's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.[0]

4.3. Justification for Dose

The CCI dosing regimens selection was based on the final analysis of the Phase 1 first-in-human study DNG1001, DNG1006 study, GLP toxicity studies, and *in vitro* and *in vivo* antiviral activity data of JNJ-64281802.

CCI



4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed the last remote follow-up assessment 6 months post first dose.

Participants who prematurely discontinue study intervention for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule. Participants who withdraw consent during the treatment or follow-up phase will be offered an optional Early Exit Visit. The optional Early Exit Visit will occur the day of consent withdrawal or as soon as possible thereafter.

5. STUDY POPULATION

It is recommended that the screening/baseline assessments are completed as quickly as possible, in order to start intake of the first dose of study intervention as soon as possible CCI [redacted] Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

Participants with primary or secondary DENV infection will be enrolled in the study. The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Criterion modified per Amendment 1

   1.1 Male or female.

2. Criterion modified per Amendment 6

   2.1 ≥18 or ≥21 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to 60 years of age, inclusive, at the time of screening.

3. Must have a body mass index (BMI) between 18 to 35 kg/m^2 (inclusive) and a body weight of ≥45 kg at screening.

4. Must have a normal 12-lead electrocardiogram (ECG) taken in triplicate at screening (machine read and/or assessed by investigator or cardiologist), including normal sinus rhythm (heart rate between 45 and 100 beats per minute [bpm], extremes included), QTcF ≤450 ms for male participants and ≤470 ms for female participants, QRS interval <110 ms, and PR interval ≤220 ms. If the results of the ECG are outside the normal ranges, the participant may be included only if the investigator judges the deviations from normal to be not clinically significant. This determination must be recorded in the participant's source documents and initialed and dated by the investigator.

5. Criterion modified per Amendment 4

   5.1 Patient with a referral note/documentation from a health care facility or practitioner indicating NS1 positive for DENV, positive NS1 rapid test at pre-screening during an ambulatory visit, or patient who tests NS1 positive at the site.

6. Participant reported a fever with an onset within the last 48 hours.

7. Criterion modified per Amendment 4

   7.1 Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Note: prior to signing the ICF for the study, participants may specifically allow for ambulatory NS1 rapid testing performed by a member of the mobile clinical team by signing the pre-screening ICF.

8. Criterion modified per Amendment 3

   8.1 Must sign a separate part of the informed consent form if he or she agrees to provide an optional sample for future exploratory research. Where local regulations require, a separate consent may be requested for the required DNA component of the study.

9. A woman of childbearing potential must have a negative serum pregnancy test at screening.

10. A woman using oral contraceptives should use an additional contraceptive method.

    Note: The interaction between JNJ-64281802 and hormone-based contraceptives has not been assessed. The efficacy of hormone-based contraceptives may be decreased when co-administered with JNJ-64281802 and therefore they should not be considered as a highly effective contraceptive method during dosing with JNJ-64281802.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

11. A woman must be (as defined in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information)

    a. Not of childbearing potential

    b. Of childbearing potential and practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until at least 90 days after last dose the end of relevant systemic exposure. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance

12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 90 days after the last dose of study intervention.

13. During the study and for a minimum of 90 days after receiving the last dose of the study intervention, a male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

14. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last dose of study intervention.

15. Criterion modified per Amendment 5

    15.1 Willing and able to adhere to the lifestyle restrictions specified in this protocol.

    Note: Retesting of abnormal values that may lead to exclusion will be allowed once without prior approval from the sponsor. Retesting to replace lost samples or broken tubes is permitted. Retesting will be performed within the screening phase. Participants with a normal value at retest may be included.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Patient with any clinical signs and symptoms for severe dengue according to the WHO criteria[0] (such as severe plasma leakage leading to shock [DSS], fluid accumulation with respiratory distress, severe bleeding, severe organ involvement).

1.2 Criterion added per Amendment 6

Patient who recalls past/prior laboratory-confirmed dengue infection and/or past/prior laboratory-confirmed dengue infection per available medical records (any PCR, NS1, IgG/IgM seroconversion).

2. Criterion modified per Amendment 4

2.1 Criterion modified per Amendment 5

2.2 Use of any CYP3A4 inducers (eg, phenytoin, rifampin), UGT1A9 inducers (eg, rifampin), or substrates for CYP3A4 with a narrow therapeutic range (eg, alfentanil, cyclosporin), CYP2C8 substrates (eg, repaglinide) or BCRP substrates (eg, pravastatin and folic acid) within 14 days before first dose of study drug.

Use of any CYP3A4 inhibitors (eg, clarithromycin, itraconazole) or UGT1A9 inhibitors (eg, probenecid, mefenamic acid) within 7 days before first dose of study drug.

2.3 Criterion modified per Amendment 6

Use of any CYP3A4 inducers (eg, phenytoin, rifampin), UGT1A9 inducers (eg, rifampin), substrates for CYP3A4 with a narrow therapeutic range (eg, alfentanil, cyclosporin), or sensitive BCRP substrates (eg, pravastatin and folic acid) from 14 days before first dose of study drug until 28 days after last dose of study drug.

Systemic use of strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole) or UGT1A9 inhibitors (eg, probenecid, mefenamic acid) from 7 days before first dose of study drug until 28 days after last dose of study drug.

3. Criterion modified per Amendment 4

3.1 One or more of the following laboratory abnormalities at screening: hematocrit >52% in males; >46% in females, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1000 U/L, absolute neutrophil count <1500/µL, platelet count <80,000/ µL, hemoglobin <12.0 g/dL in males; <10.0 g/dL in females, total bilirubin >26 µmol/L.

4. History of liver or renal insufficiency (estimated creatinine clearance below 60 mL/min) calculated by the Modification of Diet in Renal Disease [MDRD] formula][0]; significant cardiac, vascular, pulmonary, gastrointestinal (such as significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine, neurologic, hematologic, rheumatologic, psychiatric, neoplastic, autoimmune or metabolic disturbances.

5. History of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).

6. Any history of clinically significant skin disease such as, but not limited to, dermatitis, eczema, drug rash, psoriasis, food allergy, and urticaria during the last 5 years.

7. Known allergies, hypersensitivity, or intolerance to JNJ-64281802 or its excipients (refer to the IB).[0,0]

8. Taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before the planned first dose of study intervention.

9. 9.1 Criterion modified per Amendment 3

   9.2 Criterion modified per Amendment 4

   Received an investigational intervention (including investigational vaccines or Dengvaxia) or used an invasive investigational medical device within 30 days before the planned first dose of study intervention or is currently enrolled in an investigational study or is planning to be enrolled in an investigational study within 90 days after the last dose of study intervention. Participants will be allowed to receive an authorized/licensed COVID-19 vaccine at any time before, during, and after the study (see Section 10.9, Appendix 9: Guidance on Study Conduct During the COVID-19 Pandemic).

10. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.

11. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

12. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments (eg, in case of coinfections).

13. Had major surgery, (eg, requiring general anesthesia) within 4 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

14. Having donated or lost more than 1 unit of blood (500 mL) within 60 days or more than 1 unit of plasma (250 mL) within 7 days before the planned (first) dose of study

intervention or having the intention to donate blood or blood products within 90 days after (the last) dose of study intervention.

15. Known or suspected congenital or acquired immunodeficiency; or receipt of immunomodulation therapy such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).

16. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria is noted in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.3.1. Meals and Dietary Restrictions

1. Refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from enrollment until the last dose of the study intervention.

2. Criterion modified per Amendment 5

CCI [redacted]

3. Must not consume any foods or drinks (including additional salt or sugar) other than those provided by the study site personnel during domiciled inpatient periods.

5.3.2. Caffeine and Alcohol

1. Must refrain from the use of food or drinks/beverages containing alcohol, or the use of energy drinks or beverages containing caffeine from enrollment until the last dose of the study intervention.

2. Limited use of caffeinated methylxanthines (eg, coffee, tea, cola, and chocolate) is allowed (≤500 mg/day, as contained in 5 cups of tea or coffee or 8 cans of cola).

3. May not use drugs of abuse (including amphetamine, barbiturate, cannabinoids, cocaine, methadone, opiates, phencyclidine, and tricyclic antidepressants) from enrollment until 3 weeks after last dose of study drug.

5.3.3. Activity

1. Unusual strenuous exercise may affect study-specified assessments and safety laboratory results; for this reason, unusual strenuous exercise (as assessed by the investigator) should be avoided from enrollment until 30 days after last dose of study drug.

2. Must not participate in another investigational study during the study or within 90 days after last dose of study drug.

3. Avoid donating blood for at least 90 days after (the last) dose of study intervention.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

CCI [redacted]

CCI

On Study Day 1, CCI [redacted]. Intake of subsequent doses of study intervention should take place according to the Schedule of Activities and at approximately the same time each day preferably. CCI [redacted] All study intervention intakes will take place at the study site.

Description of Interventions

Arm Name	Intervention	Placebo
Intervention Name	JNJ-64281802	Placebo
Type	Drug	Placebo
Dose Formulation	CCI [redacted]	
Unit Dose Strength(s)		
Dosage Level(s)		
Route of Administration	Oral	Oral
Use	Experimental	Placebo
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container.	CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container. CCI [redacted] Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container.

Arm Name	Intervention	Placebo
Food/Fasting requirement	CCI	

Study intervention administration must be captured in the source documents and the eCRF.

JNJ-64281802 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[0,0]

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored at controlled temperatures as indicated on the product-specific labeling. Any temperature excursion must be reported to the sponsor's representative within 24 hours of knowledge of the excursion. After exposure to a temperature excursion, the product will not be used until written approval has been given by the sponsor's representative.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Randomization will be performed within CCI hours after onset of fever. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country and by the duration of dengue symptoms from onset till time of randomization (≤24 hours and >24 hours).

Blinding

To ensure participant safety while maintaining the study blind, sealed envelopes containing the study intervention identification (eg, active, placebo) will be provided to the investigator. These sealed envelopes will be kept together in a limited-access area that is accessible 24 hours per day. All envelopes, whether opened or sealed, will be collected after the end of the participant's participation in the study. The study interventions will be identical in appearance and will be packaged in identical containers.

Data that may potentially unblind the intervention assignment (ie, study intervention plasma concentrations, virologic data, study intervention preparation/accountability data, intervention allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

At the time of the first interim analysis (when at least 50 participants with a primary infection reached Day 28 or discontinued earlier) and the primary analysis (when all participants reached Day 28 or discontinued earlier), Sponsor personnel will become unblinded to the interim analysis and primary analysis data. Study site personnel, investigators, participants, and operational Sponsor team members involved with the sites will have no access to any of the evaluations performed by either the Sponsor or the DRC so that follow-up of safety during the 6-months follow-up period can still be performed in a blinded fashion.

Under normal circumstances, the blind should not be broken to the study site personnel, investigators, participants, and operational Sponsor team members until all participants have

completed the study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by opening the sealed code. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the eCRF, and in the source document.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. JNJ-64281802 will be administered orally, by designated study-site personnel at the study sites, who will check the participant's mouth to confirm that the dose was swallowed. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study intervention.

6.5. Concomitant Therapy

Prestudy therapies administered up to 14 days before first dose of study intervention must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study intervention until the end of the study. Concomitant therapies should also be recorded beyond the end of study only in conjunction with new or worsening AEs.

All therapies (prescription or over-the-counter medications [including analgesics], including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Beyond those listed below, participants are not being asked to discontinue current medications. If medical conditions not related to the study arise after dosing and dictate the use of medications,

participants are encouraged to obtain appropriate care, comply with the course of therapy as prescribed by their physician, and inform the investigator as soon as possible.

Stable hormone replacement therapy in postmenopausal female participants (ie, same dose and not starting or stopping hormone replacement therapy for 2 weeks prior to the planned [first] dose of study intervention until the end of the study) is allowed. It should be noted that JNJ-64281802 may affect the effectiveness of hormone replacement therapy agents when co-administered. The use of hormone replacement therapy should be recorded in the Concomitant Therapy Section of the CRF. Applicable procedures and treatment guidance based on package inserts should be respected.

Other comedication is allowed in the following cases:

- In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents in the recommended dose scheme is permitted.
- In case of severe nausea, the use of anti-emetics is permitted.
- In case of severe diarrhea, the use of loperamide is permitted (at ≤4x2 mg per day for a maximum of 3 consecutive days).

The following therapies are not permitted during the study and for the time period prior to screening as noted:

- Herbal supplements within 14 days prior to randomization and during the study with the exception of topically administered products.
- Participants must not use any CYP3A4 inducers (eg, phenytoin, rifampin), UGT1A9 inducers (eg, rifampin), substrates for CYP3A4 with a narrow therapeutic range (eg, alfentanil, cyclosporin), or sensitive BCRP substrates (eg, pravastatin and folic acid) from 14 days before first dose of study drug until 28 days after last dose of study drug. The systemic use of strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole) or UGT1A9 inhibitors (eg, probenecid, mefenamic acid) is not allowed from 7 days before first dose of study drug until 28 days after last dose of study drug. In case any of these inhibitors or substrates are used, the date and time of dosing, the indication, the dose, and the dosing regimen must be recorded in the Concomitant Therapy Section of the CRF.
- Participants must not use any aspirin or NSAIDs, including ADVIL®, MOTRIN®, NUPRIN®, ALEVE®, NAPROXEN®, and CELEBREX® and any anticoagulant drugs (eg, warfarin or clopidogrel), from 7 days before first dose until 28 days after the last dose or through 7 days after hospital discharge, whichever is later. Aspirin, NSAIDs and anticoagulants can interfere with the ability of the blood to clot. The investigators may recommend paracetamol/acetaminophen or an equivalent, which can be used safely for fevers and body aches.
- Participants must not use any immunosuppressive corticosteroids (excluding topical and nasal) or immunosuppressive drugs from 3 months before first dose of study drug until 28 days after last dose of study drug. An immunosuppressive dose of corticosteroids is defined as ≥10 mg prednisone equivalent per day for ≥14 days. In case immunosuppressive corticosteroids or immunosuppressive drugs are used, the date and time of dosing, the

indication, the dose, and the dosing regimen must be recorded in the Concomitant Therapy Section of the CRF.

Participants will be allowed to receive an authorized/licensed COVID-19 vaccine at any time before, during, and after the study (see Section 10.9, Appendix 9: Guidance on Study Conduct During the COVID-19 Pandemic).For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition (relative to the moment of signed ICF), the condition must be documented in the Adverse Event Section of the CRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.6. Dose Modification

Any dose/dosage adjustment not planned per protocol should be overseen by medically qualified study-site personnel (principal or sub-investigator unless an immediate safety risk appears to be present).

6.7. Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, an AE) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant

If a participant discontinues study intervention for any reason (except withdrawal of consent) before the end of the double-blind treatment phase, the participant will be asked to continue with their remaining study visits and assessment schedule. Participants who withdraw consent during the treatment or follow-up phase, will be offered an optional Early Exit Visit. The optional Early Exit Visit will occur on the day of consent withdrawal or as soon as possible thereafter and will consist of the same assessments as at the Day 28 follow-up visit.

Additional participants may be entered only for those participants who discontinued study drug before last dose of study drug on Day 2 to ensure the protocol-specified number of participants complete the study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed (except in the case of an optional Early Exit Visit).

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

7.2.1. Withdrawal from the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research sample.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile[0]. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of antiviral activity, PK, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, vital signs, blood sampling (except at screening). Blood collections for PK and antiviral activity assessments and all other assessments (eg, ECG, vital signs, physical examination) should be performed within the time window defined in the Schedule of Activities. Actual dates and times of assessments will be recorded in the source documentation and CRF.

Additional serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume for the study is approximately 389.8 mL for males and 392.3 mL for females.

Refer to Table 1 for details.

Table 1: Volume of Blood to be Collected From Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Pharmacokinetics	3	17	51 mL
Safety (including screening and post-intervention assessments)			
- Hematology	3	9	27 mL
- Serum chemistry[b]	8	9	72 mL
- Coagulation	2.7	9	24.3 mL
- Serum pregnancy	2.5	1	2.5 mL
- NS1 rapid test[h]	0.5	1	0.5 mL
Viral load			
- RT Qualitative PCR [c]			
- RT Quantitative PCR + back-up			
- Plaque assay			
- NS1 testing			
Humoral Immunity	10	11 [d]	110 mL[e]
- IgG			
- IgM			
- nAb			
Viral Genome Sequencing (Viremics)			
Serum proteins (including cytokines)			
Cellular Immunity	30[i]	2	60[i] mL
Host RNA	2.5	8	20 mL
Blood sample collection for plasma protein binding	3	3	9 mL
Blood sample collection for alpha-1 acid glycoprotein	2.5	3	7.5 mL
Pharmacogenomic sample	8.5	1	8.5 mL
Approximate Total[f]			389.8 mL (for males)/ 392.3 mL (for females)[g]

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Serum chemistry includes hematology and biochemistry (including glucose).
c. Retrospective analysis of the screening samples will be performed.
d. Maximum 14 samples will be collected in case repeat required at D1 and in case prolongation stay at unit until Day 9.
e. Includes viral load, humoral immunity, serum proteins (including cytokines) and viral genome sequencing
f. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
g. Additional 87.6 mL of blood per participant will be collected in case of an extended stay at the inpatient facility from Day 6 to Day 9.
h. At pre-screening or at screening, if not yet performed by a health care facility or practitioner as part of standard of care.
i. Volume per blood sample can be reduced from 30 mL to 10 mL at Day 28, subject to the local regulations and investigator's decision.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- eDC Manual
- eSource Manual
- Sample ICF

8.1. Antiviral activity Assessments

At time points specified in the Schedule of Activities, blood samples will be obtained for measurement of:

- levels of DENV RNA
- levels of viremia (ie, infectious virus)
- DENV NS1 protein

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of the DENV infection and antiviral activity of the study intervention, including viral genotypic and phenotypic assessments.

Procedures for sample collection, processing and storage will be provided in the laboratory manual.

DENV RNA levels will be assessed using a validated quantitative DENV RT-PCR assay.

DENV viremia (ie, level of infectious DENV) will be determined using an assay for infectious virus quantification such as a plaque assay.

In addition, antiviral activity will be explored by assessing NS1 protein using an NS1 test. Confirmation of DENV infection will be done retrospectively using qualitative PCR after screening.

8.1.1. Viral Genome Sequencing

Viral genome sequencing analysis will be performed by sequencing the NS4B gene and other regions of the DENV genome (if warranted) to characterize emerging DENV variants associated with resistance to JNJ-64281802.

Sequencing of the DENV genome will be performed to monitor DENV variants present at the time points indicated in the Schedule of Activities, at the discretion of the sponsor's virologist.

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of DENV infection and antiviral activity and safety of JNJ-64281802, including viral genotypic and phenotypic assessments.

8.2. Safety Assessments

Details regarding the internal DRC are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

Key safety assessments will include the monitoring of AEs (including DENV infection-associated AEs), physical examinations, vital signs, and clinical safety laboratory tests.

Adverse events will be reported and followed by the investigator as specified in Section 8.2.4.1, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF and in the source documentation.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Physical Examinations

A clinical status check should be performed within 30 minutes before the first study drug administration.

A complete physical examination (head/neck/thyroid; eyes/ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological) will be performed at screening and on Day 28. At Days 3, 6, 14, and 21, only an abbreviated physical exam (respiratory, cardiovascular, skin, abdomen) will be performed. At Days 1, 2, 4, 5, 7, 8, and 9, a physical examination may be performed at the investigator's discretion. Body weight will be

measured daily from screening until Day 6 and during on site follow-up visits, and height will be measured at screening only.

To obtain the actual body weight, participants must be weighed lightly clothed. The height should be measured barefoot at the screening visit.

Any clinically relevant changes occurring during the study must be recorded in the Adverse Event Section of the CRF and in the source documentation.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, peripheral capillary oxygen saturation (spO2) (not at screening), input-output (I/O) ratio (not at screening) and blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology and coagulation will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

8.2.4.1. Assessment of Clinical Endpoints

Leukocyte and Platelet Counts

Blood samples will be obtained for measurement of leukocyte and platelet levels at time points specified in the Schedule of Activities.

Hematocrit Concentration

Blood samples will be obtained for the measurement of hematocrit concentration, at time points specified in the Schedule of Activities.

Any participant who has a hematocrit rise with values >20% of the baseline at any timepoint will require full blood count (FBC) monitoring every 4 hours (at the discretion of the investigator).

8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated main study ICF is obtained until completion of the participant's last study-related procedure. No AEs will be reported for participants who only signed a pre-screening (diagnostic) ICF and who were not enrolled in the main study.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. For participants with only a signed pre-screening (diagnostic) ICF (ie, for whom consent was not given to enroll in the main study by signing the main ICF), no AEs procedure will be reported. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Signs and symptoms of DENV infection (DENV-infection associated AEs) will be collected by the investigator as solicited AEs. DENV infection signs and symptoms checklist may be compiled by any delegated study team member, and it may be used to assist in the collection of DENV infection associated AEs.

Solicited AEs are predefined events for which the participant is specifically questioned (Table 2). All AEs are evaluated using the gradings presented in Table 3, the US FDA Toxicity Grading Table in Section 10.6, Appendix 6, or the rash management protocol in Section 10.7, Appendix 7.

Table 2: Solicited Adverse Events

Systemic Reactogenicity	Laboratory Events
- Retro-orbital pain [a]	- Decreased Hemoglobin [b]
- Abdominal Pain [a]	- Neutropenia [b]
- Arthralgia [a]	- Elevated ALT [b]
- Fever [b]	- Thrombocytopenia [b]
- Headache [b]	- Leukocytosis [b]
- Nausea [b]	- Prolonged PT/INR [b]
- Fatigue [b]	- Prolonged PTT [b]
- Myalgia [b]	
- Loss of Appetite [a]	
- Vomiting [b]	
- Diarrhea [b]	
- Rash [c]	

ALT = alanine aminotransferase; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

[a] Grading according to Table 3

[b] Grading according to the FDA Toxicity Grading Table in Section 10.5, Appendix 5.

[c] Grading according to the rash management protocol in Section 10.7, Appendix 7.

Table 3: Grading of Solicited Adverse Events

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Retro-orbital pain, Arthralgia, Abdominal pain,	Event that is easily tolerated, may require 1 dose of medication/treatment	Event that interferes with daily activity or requires >1 dose of medication/treatment	Event that prevents daily activity	Life-threatening
Loss of appetite	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g. inadequate oral caloric intake and/or fluid intake); tube feeding or TPN indicated	Life threatening consequences; urgent intervention indicated

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study will promptly discontinue further study intervention but will continue study visits for additional safety follow-up.

Follow-up information regarding the outcome of the pregnancy will be required.

8.4. Treatment of Overdose

For this study, any dose of JNJ-64281802 greater than the assigned daily dose within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until JNJ-64281802 can no longer be detected systemically (at least 46 days).
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Venous blood samples will be used to evaluate the PK of JNJ-64281802. Plasma collected for PK may additionally be used to evaluate safety, pharmacokinetic (plasma protein binding, metabolites) or antiviral activity aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples will be collected for measurement of plasma concentrations of JNJ-64281802 at timepoints specified in the Schedule of Activities, and processed, handled and identified according to the laboratory manual, which will be provided before the start of the study. The exact dates and times of blood sampling must be recorded in the eCRF or laboratory requisition form.

8.5.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of JNJ-64281802 using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the Sponsor's Bioanalytical Laboratory Department of Bioanalysis.

Pharmacokinetic samples from participants receiving placebo will not be analyzed unless unexpected results should occur.

To allow selection of samples, the bioanalytical laboratory will receive randomization lists per treatment. Unblinding of the randomization code will be performed at the bioanalytical laboratory only and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the execution of the study.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of protein binding, biomarkers or the metabolite profile.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

The following PK parameters will be derived for JNJ-64281802:

- area under the concentration curve during one dosing interval (AUC_{τ}) (if data allows)
- pre-dose concentration (C_{trough}) and
- maximum observed plasma concentration (C_{max}) (if data allows).

Actual sampling times will be checked for major aberrations. In case a major aberration occurs for an actual sampling time of >20.00% deviation from the scheduled time, this plasma concentration will be excluded from descriptive statistics in the plasma concentration table.

In a subset of 20 participants, total JNJ-64281802 plasma concentration, the fraction unbound (fu) of JNJ-64281802 and alpha-1 acid glycoprotein may be determined at selected time points, as indicated in the Schedule of Activities to assess protein binding at the discretion of the sponsor.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-64281802 will be derived.

Pharmacokinetic/Pharmacodynamic Evaluations

Pharmacokinetic-pharmacodynamic evaluations may be performed to evaluate the relationship between the PK and the antiviral activity of JNJ-64281802, as data allow.

In addition, the relationship between the PK and selected safety endpoints may be explored, as data allow and at the discretion of the sponsor.

8.6. Genetics

A blood sample will be collected from all participants for the pharmacogenomic component of the study.

8.6.1. Human Leucocyte Antigen Typing and Pharmacogenomics Assessments

One blood sample for human leucocyte antigen (HLA) typing and for pharmacogenomics (DNA) research will be taken, preferably at baseline (ie, before first dose of study intervention). This sample can be used to determine the HLA type of the participant. In addition, this sample can be used to investigate the potential association of genetic factors with PK, antiviral activity or safety of JNJ-64281802 or the DENV infection.

These analyses may be conducted under the supervision of the sponsor and may be reported separately from the main study report. If necessary, the sample may be collected at a later time point without constituting a protocol deviation.

8.7. Biomarkers

The study includes collection of blood samples for exploratory analysis. Sampling will be performed for all participants at the time points indicated in the Schedule of Activities.

Samples for host RNA might be used for transcriptional profiling for example using microarray technology. Serum samples for protein analyses might be analyzed using assays such as ELISA or Luminex.

Examples of analytes that could be investigated by mRNA assessment and/or protein measurements include, but are not limited to, ISG-15, interleukin (IL)-2, IL-6, IL-8, IL-10, IL-12, IL-15, IL-18, tumor necrosis factor (TNF)-α, IFN-γ, and chemokine (C-X-C motif) ligand 10 (CXCL10, also referred to as interferon-inducible protein 10 [IP-10]).

Samples can only be used for research related to JNJ-64281802 or DENV infection or may be used to develop tests/assays related to JNJ-64281802 or DENV infection.

8.8. Immune Assessments

8.8.1. Humoral Immune Response

Blood samples will be obtained for the assessment of antibody response. Anti-DENV IgG and IgM will be measured using an in-house developed or commercial ELISA and the IgG pattern will be used to make a distinction between primary and secondary dengue infection. Presence of neutralizing antibodies against DENV will be determined using an assay such as flow cytometry-based neutralization assay.

8.8.2. Cellular Immune Response

Peripheral blood mononuclear cell (PBMC) samples may be analyzed in a subset of participants to assess DENV-specific T and B cell immune responses by assays such as enzyme-linked immunospot assay (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with DENV-specific antigens. ELISpot detects T cells that secrete gamma interferon (IFN-γ) or B cells that secreted IgG and/or IgM in response to an antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ T cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs by flow cytometry or other methods including but not limited to CyTOF, to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research related to DENV infection or JNJ-64281802 (safety/antiviral activity).

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the antiviral activity and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to reduction in viral load in participants with a primary DENV infection, as measured by area under the log10-transformed DENV RNA viral load curve from baseline on Day 1 until Day 5.

9.2. Sample Size Determination

The study will recruit in total 150 participants, with the primary objective of investigating the antiviral activity of JNJ-64281802 versus placebo based on DENV RNA in primary DENV infection and with an objective to describe the safety and tolerability of JNJ-64281802 in participants with DENV infection. The sample size can be revised after an interim analysis on the proportion of primary versus secondary DENV infections (refer to Section 9.5, Interim Analysis).

For the objective of antiviral activity in participants with a primary DENV infection, the hypothesis is that the intervention effect is superior to placebo as measured on the DENV RNA $\log_{10}$ viral load curve from baseline on Day 1 until Day 5.

To assess sample size requirements for this hypothesis, data of 47 DENV RNA curves were estimated similar to the DENV RNA curves graphically presented in the balapiravir trial. All curves were considered as balapiravir did not have an effect on the viral load. A limit of detection of 2.3 log copies/mL was assumed. Although the majority of the population included in the balapiravir trial suffered from a secondary infection[0], these estimated DENV RNA curves were considered representative for a primary infected dengue population. As the clearance of DENV RNA occurs earlier and faster in patients with secondary dengue, this is a conservative assumption.[0]

The 47 estimated DENV RNA curves were used to calculate the means, standard deviations and correlations of the $\log_{10}$ viral loads over time. These calculated values were thereafter used to simulate 10,000 trials, each with a sample size of 80 participants. A treatment effect of 0.30 $\log_{10}$ copies/mL per day DENV RNA clearance on top of placebo, or two-fold reduction of the viral load was applied. Based on these 10,000 simulated trials and using a general linear model with treatment regimen as fixed factor and baseline $\log_{10}$ viral load as a covariate, a sample size of 80 participants (40 per group) was estimated to provide a power of at least 80% at the one-sided 5% significance level to detect an intervention effect of 0.30 $\log_{10}$ copies/day additional DENV RNA clearance when compared to placebo.

The specificity of the DENV NS1 testing at baseline is estimated to be 98% which entails that 2% of participants that will be enrolled will not be evaluable for efficacy. Based on literature,[0] it is estimated that approximately 60% of the total population will have a primary infection. Furthermore, it is anticipated that approximately 4% of the enrolled participants drop-out for other

reasons. The study will therefore need to recruit a total of 150 participants in order to achieve a sample of 84 participants to achieve >80% power on the primary hypothesis.

For the objective of safety assessment, the probability was calculated to observe an (S)AE that has a true incidence of 1% which would be 53% with a total sample size of 75 participants on active treatment; the probability to observe an (S)AE with a true incidence of 0.1%, 0.5% and 0.8% is 7%, 31% and 45%, respectively.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the informed consent form
Randomized	All participants who were randomized into the study
Safety	All randomized participants who take at least 1 dose of study intervention.
PK	All participants who receive at least 1 dose of study drug and who have at least 1 plasma concentration data value after dosing.
Intent-to-treat infected (ITT-i)	All randomized participants with a DENV infection who received at least one dose of the study intervention
Per-protocol	All participants who are included in the ITT-I population without protocol violations that affect the antiviral activity assessment.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to interim database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Exploratory subgroup analysis can be performed for the different drug formulations used in the trial.

9.4.1. General Considerations

Participants will be classified prior to data base lock as being non-DENV infected, primary DENV infected or secondary DENV infected based on all available virological information. The decision whether the participant had a primary or secondary infection will be based on the IgG profile.

An interim analysis will be performed when at least 50 participants with a primary dengue infection reached Day 28 or discontinued earlier. Based on the results of this analysis, the DRC and study team can take the decision to stop the trial for futility.

The primary analysis will be performed when all participants reached Day 28 or discontinued earlier. A one-sided test at the 5% significance level will be used for the hypothesis that JNJ-64281802 is superior to placebo in participants with a primary infection.

The final analysis will be performed when the last visit of the last participant in the study occurred.

9.4.2. Antiviral Activity Analysis

The intent-to-treat infected (ITT-i) population will be used for all antiviral activity analyses. Treatment assignment for this population will be defined by actual treatment received.

9.4.2.1. Primary Endpoint(s)

The difference in area under the log_{10}-transformed DENV RNA viral load curves from immediately prior to first dose (baseline) until Day 5 for JNJ-64281802 versus placebo dosing will be derived from a mixed model with treatment regimen and the stratification factors as fixed factors and baseline log_{10} viral load as a covariate, calculating least square mean differences, including the 90% 2-sided confidence intervals in the ITT-I population with a primary dengue infection based on IgG profile.

9.4.2.2. Secondary Endpoint(s)

Descriptive statistics and mean (and standard error) graphs will be shown for the log_{10} DENV RNA and viremia actual values and changes from baseline over time in participants with primary DENV infection.

In participants with primary DENV infection, the proportion of participants within the DENV RNA and viremia categories (≥lower limit of quantification [LLOQ], <LLOQ target detected and, <limit of detection [LOD] target not detected) will be shown in a frequency tabulation per analysis time point.

Time to undetectable DENV RNA/viremia will be analysed using Kaplan-Meier estimates analysis. A summary table including number of participants with primary DENV infection included in the analysis, number of participants censored, 25^{th} and 75^{th} percentiles and median time-to event, with 95% confidence intervals based on log-log transformation method, will be presented. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by treatment.

Descriptive statistics will also be used to describe the IgM and IgG response. The proportion of participants with antibody positivity and the titer and timing of the antibody response will be determined. Descriptive statistics will include sample size, mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum.

9.4.3. Safety Analyses

All participants enrolled into the study who received at least one dose of study intervention will be included in the safety population. Participants in this population will be defined by the study intervention actually received, not by randomization assignment. The safety population will be used for all safety analyses.

Safety data will be presented descriptively. No statistical testing of safety data is planned.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 20 days is considered to be treatment emergent. All reported adverse events will be included in the analysis. For each

adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the initial ECG will be used as baseline). Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Vital Signs

Vital signs including pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Physical examination findings will be summarized at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.4.4. Immune Analysis

9.4.4.1. Humoral Immune Analyses

Please refer to Section 9.4.4.2 for the analysis of the IgM and IgG response.

Descriptive statistics will be used to describe the neutralizing antibody response. The proportion of participants with antibody positivity, including neutralizing antibodies for all 4 DENV serotypes, and the titer and timing of the antibody response will be determined.

Descriptive statistics will include sample size, mean, SD, CV, geometric mean, median, minimum, and maximum.

9.4.4.2. Cellular Immune Analyses

Descriptive statistics will be used to describe the magnitude of the IFN-γ T cell response or the CD4+ and CD8+ T cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any antigen) or B cell response as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) will also be tabulated for PBMCs during the dosing and on-site follow-up phase (Day 28, optional). The proportion of participants with positive responses based on the magnitude of the IFN-γ T cell response or the CD4+ or CD8+ T cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the antigens as defined by ELISpot and/or ICS, respectively, or B cells that secrete IgG and/or IgM will be determined.

Descriptive statistics will include sample size, mean, SD, CV, geometric mean, median, minimum, and maximum.

9.4.5. Pharmacokinetic Analyses

All participants having received at least one dose of study intervention and having at least one PK parameter value will be included in the PK analysis. All participants having received at least one dose of study intervention and having at least one plasma concentration data value after administration will be included in the descriptive statistics.

Descriptive statistics will be calculated for the plasma concentrations of JNJ-64281802 and for the derived PK parameters, as applicable. Statistics include sample size (n), mean, SD, CV, geometric mean, median, minimum, and maximum.

For each participant, plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis including various transformations in order to get a general overview.

Special attention will be paid to the plasma concentrations and PK parameters of those participants who have discontinued the study for an AE, or who experienced an AE of at least grade 3, or a serious adverse event (SAE).

Endpoints and analyses related to PK are:

- PK parameters of JNJ-64281802 in plasma
- Relationship between one or more PK parameters and antiviral activity endpoints (eg, DENV RNA AUC)
- Relationship between one or more PK parameters and safety data, at the discretion of the sponsor.

If deemed necessary, population PK analysis of plasma concentration-time data of JNJ-64281802 may be performed using nonlinear mixed-effects modelling. A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be included in a population PK analysis. Samples collected after the snapshot date may be included in a population PK re-analysis at a later date. If conducted, details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-64281802 as applicable, with selected antiviral activity and with selected safety endpoints may be evaluated, applying graphical tools and, if feasible, statistical models, as data allow. If conducted, analysis results of the relationship between the PK and selected safety endpoints will be presented in a separate report.

9.4.7. Biomarkers Analyses

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between participants. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented in the clinical study report or a separate report.

9.4.8. Viral Genome Sequence Analyses

The results of DENV viral genome sequencing will be evaluated by the sponsor virologist. Relevant changes in the DENV genome will be tabulated and described for participants with detectable DENV RNA during the study period.

Additional exploratory characterization of the DENV viral genome sequence and phenotype may be performed and reported separately.

9.4.9. Human Leukocyte Antigen Typing and Pharmacogenomic Analyses

The statistical approach for analysing the exploratory host DNA research may depend on the objective of the analyses (antiviral activity, safety, and PK) and possibly relevant genes at the time of analysis. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented in the clinical study report or a separate report.

9.5. Interim Analysis

An interim analysis will be performed when at least 50 participants with a primary dengue infection reached Day 28 or discontinued earlier to check for futility. Conditional power values will be calculated using the observed data and assuming that in the remainder of the trial the effect size used for the sample size calculation will be present. The conditional power provides quantification of the likelihood that the study intervention will ultimately be successful, ie the probability of claiming a study intervention effect at the completion of the study based on the available interim data. A futility stopping boundary of 25% for the conditional power will be used. This is considered a conservative boundary also reflecting that in this early stage of development it may be best to complete the study to have a larger database to draw conclusions from. In case

the probability of a successful trial is lower than the futility boundary, the DRC and study team can take the decision to stop for futility after evaluation of all available data. Assuming the outcome for the primary endpoint as used for the sample size calculations was true, with a treatment effect of 0.30 log10 copies/mL per day DENV RNA clearance on top of placebo, the chance of reaching the futility stopping boundary at the time of the IA is at most 5%. Otherwise, if there is no treatment effect at all, the chance of reaching the futility stopping boundary is at least 60%. The proportion of primary infections will be assessed as well during this interim analysis. If the proportion is lower than expected 60%, the sample size may be increased.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

9.6. Data Review Committee

An internal DRC will be established as noted in Committees Structure in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	adverse event
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma analyte concentration-time curve
β-hCG	beta-human chorionic gonadotropin
bid	twice daily
BMI	body mass index
BQL	below quantification limit
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CN	cyanide
COVID-19	coronavirus disease 2019
CRC	clinical research coordinator
CRF	Case Report Form
CTCM	Ca^{2+} transient measured in human cardiomyocytes
CV	coefficient of variation
CYP	cytochrome P450
D	dose
DBP	diastolic blood pressure
DENV	dengue virus
DHF	dengue hemorrhagic fever
DSS	dengue shock syndrome
DLT	dose limiting toxicity
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
DRC	data review committee
DRM	data review meeting
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC_{50}	50% effective concentration
ECG	electrocardiogram
eDC	electronic Data Capture
EMA	European Medicines Agency
eSource	electronic source data
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
f_u	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GP	general practitioner
GSH	glutathione
hAhR	human aryl hydrocarbon receptor
HCC	healthcare center
HCP	healthcare provider
HDL	high-density lipoprotein
hERG	human ether-à-go-go-
HLA	human leukocyte antigen
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation

IEC	Independent Ethics Committee
INR	international normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT-i	intent-to-treat infected
i.v.	intravenous(ly)
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry
LDH	lactic dehydrogenase
LDL	low-density lipoprotein
LOD	limit of detection
LS	least square
MD	medical doctor
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MEC	minimal effective concentration
MTD	maximum tolerated dose
n	sample size
NOAEL	no observed adverse effect level
NS1	non-structural 1 protein
NS4B	non-structural protein 4B
PEG400	polyethylene glycol 400
PFU	plaque forming units
P-gp	P-glycoprotein
PK	pharmacokinetic
PQC	product quality complaint
Pre-IND	Pre-Investigational New Drug application
PT	prothrombin time
qd	once daily
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SPF	skin protection factor
SUSAR	suspected unexpected serious adverse reactions
UGT	UDP-glucuronosyltransferase
ULN	upper limit of laboratory normal range
US	United States
UV	ultraviolet
WBC	white blood cell
WHO	World Health Organization

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.
AUC_{τ}	area under the concentration curve during one dosing interval
C_{max}	maximum observed analyte concentration
C_{trough}	observed analyte concentration just prior to the beginning or at the end of a dosing interval;

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit Prothrombin time International normalized ratio (INR) Activated partial thromboplastin time	RBC Indices: MCV MCH % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose (nonfasting) Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT)		Direct bilirubin Alkaline phosphatase Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) C-reactive protein (CRP) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium
Other Screening Tests	Serum Pregnancy Testing for women of childbearing potential only		

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for future research and for the corresponding consent must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Prior to signing the ICF for the study, participants may specifically allow for ambulatory NS1 rapid testing performed by a member of the mobile clinical team by signing the pre-screening (diagnostic) ICF.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not

affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants will be asked for consent to provide optional samples for future research. After informed consent for the study is appropriately obtained, the participant or his or her legally acceptable representative will be asked to sign and personally date a separate part in the ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Where local regulations require, a separate consent may be requested for the required DNA component of the study.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-64281802 to understand dengue pathology, to understand differential intervention responders, and to develop tests/assays related to JNJ-64281802 and antiviral activity. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples). In such cases, the samples will be discarded after the initial sample storage and analysis process.

COMMITTEES STRUCTURE

Data Review Committee

An internal DRC will be established to ensure the continuing safety of the participants enrolled in this study. This committee will consist of a Global Medical Safety (GMS) therapeutic area safety head, a clinician, a clinical pharmacologist, a virologist, and a statistician, none of whom will be part of the study team or involved in the conduct of the study.

Any deaths related to dengue, admission to the intensive care unit or severe dengue (DHF/DSS) will trigger a safety data review by the DRC. If, in the judgment of the investigator and/or the sponsor's study-responsible physician, a significant or unexpected safety event occurs, the DRC will review unblinded safety data. Quarterly (every 3 months or when 50 participants are enrolled, whichever comes first), a DRC safety analysis where DRC members review unblinded data, will take place. After the review, the DRC will make recommendations regarding the continuation of the study. The DRC responsibilities, authorities, and procedures will be documented in its charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-64281802 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-64281802, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been

submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into

CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and antiviral activity parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or another equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- History of smoking or all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site

- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The sponsor will use a combination of monitoring techniques central, remote, and mainly on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study

records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must 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 investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event

must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-64281802, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all adverse events (AE).

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

An assessment of severity grade will be made using the general categorical descriptors outlined in the US FDA Toxicity Grading Table in Section 10.6, Appendix 6, and using the rash management protocol in Section 10.7, Appendix 7.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study drug, is considered an SAE.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and antiviral activity of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: United States Food and Drug Administration Toxicity Grading Table

Source: the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007)

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	>40 >104.0
Tachycardia - beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

* Participant should be at rest for all vital sign measurements.
** Oral temperature: no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/Vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or <400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or >800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B: Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	<125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	>150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	>5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	<3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	<45
Glucose – Hyperglycemia Fasting mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	>31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	>2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	<7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	>12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	<0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	<1.6
CPK – mg/dL	1.25 – 1.5x ULN***	1.6 – 3.0x ULN	3.1 –10x ULN	>10x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	<2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	<5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0x ULN	2.1 – 3.0x ULN	3.1 – 10x ULN	>10x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5x ULN	2.6 – 5.0x ULN	5.1 – 10x ULN	>10x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25x ULN	1.26 – 1.5x ULN	1.51 – 1.75x ULN	>1.75x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5x ULN	1.6 – 2.0x ULN	2.0 – 3.0x ULN	>3.0x ULN
Cholesterol	201 – 210	211 – 225	>226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5x ULN	1.6 – 2.0x ULN	2.1 – 5.0x ULN	>5.0x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cell/mm^3	650 – 1,500	1,501 – 5,000	>5,000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10x ULN**	1.11 – 1.20x ULN	1.21 – 1.25x ULN	>1.25x ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2x ULN	1.21 – 1.4x ULN	1.41 – 1.5x ULN	>1.5x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	>600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	<100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	>50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

10.7. Appendix 7: Rash Management

Dengue symptomatic infection is known to result in skin rashes in a majority of patients.[0] Rash may potentially also be related to the study drug and it may not be possible to differentiate between a rash secondary to DENV infection and one related to the study drug.

During the study, all rashes, where a causal relationship between the rash and the study drug cannot be excluded, will be discussed between the investigator and the Sponsor. I**n case a causal relationship between the rash and the study drug cannot be excluded, then the following visits and assessments will be performed as indicated**. Unscheduled follow-up visits for close follow-up of rash will be performed based on the grade (severity) of the rash. At the investigator's discretion, additional visits and assessments can be performed.

The rash event should be captured in the Adverse Event Section of the CRF, and in more detail in the specific rash assessment pages of the CRF.

If a causal relationship between the rash and the study drug cannot be excluded, safety blood samples need to be taken during the (unscheduled) visits as described below. The following parameters need to be tested: AST, ALT, creatinine, erythrocyte sedimentation rate, and a complete blood cell count (including hemoglobin, hematocrit, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Participants should be informed that they should contact the investigator and visit the study site immediately (unscheduled visit, Day 0 of the rash) when they notice any rash. They should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic sign or symptoms appear, or if mucosal involvement develops.

Monitoring of the evolution of rash events will be performed as described in Table 4 below. The following grades are based on the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. (July 2017)[a] with adaptations made by the sponsor.

[a] DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, dated July 2017. Available at https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (accessed 20 April 2019)

Table 4: Management of Rash Events by Severity Grade

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 1 rash[b]	Localized rash that is easily tolerated and/or may require one dose of medication.	Study drug intake may be continued at the investigator's discretion.	Day 0: required on-site unscheduled visit for initial rash evaluation, if participant is outside the study site. • Safety laboratory assessments are required. • Digital pictures[d] should be taken (preferred within 24 hours) after the onset of the rash. • Cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents may be prescribed. Day 1: safety blood samples and digital pictures[d] should be taken. After Day 7: If the rash is unresolved, additional unscheduled visits can be performed at the investigator's discretion. In case the rash evolves from a Grade 1 to a higher grade, additional unscheduled visits have to be conducted according to the guidelines for Grade 2 or Grade 3-4 rash, respectively. Upon resolution/stabilization of the rash: digital pictures[d] should be taken and the final rash assessment pages of the eCRF should be completed.	Not required

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 2 rash[b]	Diffuse, maculopapular rash, or target lesions. Symptomatic (pain/pruritus) but does not interfere with function and/or requires more than one dose of medication.	Study drug intake may be continued at the investigator's discretion	Day 0: required on-site unscheduled visit for initial rash evaluation, if participant is outside the study site. • Safety laboratory assessments are required. • Digital pictures[d] of skin lesions should be taken (preferred within 24 hours) after the onset of the rash. • Cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents may be prescribed. Day 1 and 7: safety blood samples and digital pictures[d] should be taken. After Day 7: If the rash is unresolved: • If there is an increase in AST/ALT of ≥2 times the ULN, participants should be followed weekly (or more frequently, at the investigator's discretion) with repeated local laboratory assessments and digital pictures[d] until resolution of the AST/ALT abnormalities. • If there is no increase in AST/ALT, additional unscheduled visits (including local laboratory assessments and digital pictures[d]) can be performed at the investigator's discretion. If the rash evolves from a Grade 2 to a Grade 3-4 rash, additional unscheduled visits have to be conducted according to the guidelines for Grade 3-4 rash Upon resolution/stabilization of the rash: digital pictures[d] should be taken and the final rash assessment pages of the eCRF should be completed	Not required

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 3 rash[b]	Diffuse rash AND vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to 1 site, OR elevations in AST/ALT >2x ULN, OR body temperature ≥39.3°C to <40.0°C (≥102.7°F to <104.0°F), OR eosinophils >1000/mm3, OR serum sickness-like reaction.	Must permanently discontinue and be withdrawn from the study; no rechallenge allowed.	Day 0: required on-site unscheduled visit for initial rash evaluation, if participant is outside the study site. Day 0 and 1: • Safety laboratory assessments are required. • Digital pictures[d] of skin lesions should be taken within 24 hours after the onset of the rash and on Day 1. Further visit(s): appropriate management and follow-up required until resolution of rash or until clinical stability is reached. Days 2, 3, and 4: *Only* if the participant's AST/ALT on Day 0 and/or Day 1 of rash >2x ULN and/or in case of rash progression: • Additional safety blood samples are required. • Digital pictures[d] are to be taken. Day 5: R*egardless* of the Day 0/1 AST/ALT levels or rash progression: • Additional safety blood samples are required. • Digital pictures[d] are to be taken. After Day 5: Weekly follow-up visits are required (or more frequently at the investigator's discretion) as long as Grade 3-4 rash is present. Once Grade 3-4 rash has resolved to ≤Grade 2 rash, follow-up should be done according to the instructions for follow-up visits for Grade 1 or Grade 2 rash, respectively. • Only if the participant's AST/ALT on Day 5 of rash is still >2x ULN and/or in case of rash progression, additional safety blood samples and digital pictures[d] are required at these weekly follow-up visits, until resolution or stabilization of the AST/ALT elevations. Upon resolution/stabilization of the rash: digital pictures[d] should be taken and the final rash assessment pages of the eCRF should be completed.	Required[c] Biopsy required within 24hrs after onset of rash.

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 4 rash[b]	Potentially life-threatening rash with: Extensive or generalized bullous lesions, OR ulceration of mucous membrane involving two or more distinct mucosal sites, OR Stevens-Johnson syndrome, OR toxic epidermal necrolysis.	Must permanently discontinue and be withdrawn from the study; no rechallenge allowed.	Day 0: required on-site unscheduled visit for initial rash evaluation, if participant is outside the study site. Day 0 and 1: • Safety laboratory assessments are required. • Digital pictures[d] of skin lesions should be taken within 24 hours after the onset of the rash and on Day 1. Further visit(s): appropriate management and follow-up required until resolution of rash or until clinical stability is reached. Days 2, 3, and 4: *Only* if the participant's AST/ALT on Day 0 and/or Day 1 of rash >2x ULN and/or in case of rash progression: • Additional safety blood samples are required. • Digital pictures[d] are to be taken. Day 5: R*egardless* of the Day 0/1 AST/ALT levels or rash progression: • Additional safety blood samples are required. • Digital pictures[d] are to be taken. After Day 5: Weekly follow-up visits are required (or more frequently at the investigator's discretion) as long as Grade 3-4 rash is present. Once Grade 3-4 rash has resolved to ≤Grade 2 rash, follow-up should be done according to the instructions for follow-up visits for Grade 1 or Grade 2 rash, respectively. • Only if the participant's AST/ALT on Day 5 of rash is still >2x ULN and/or in case of rash progression additional safety blood samples and digital pictures[d] are required at these weekly follow-up visits, until resolution or stabilization of the AST/ALT elevations. Upon resolution/stabilization of the rash: digital pictures[d] should be taken and the final rash assessment pages of the eCRF should be completed.	Required[c] Biopsy required within 24hrs after onset of rash.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase

a. Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the participant. The initial visit should be conducted as soon as possible after the participant contacts the investigator to report the AE (ie, preferably on Day 0). The initial visit and subsequent visits to manage the rash may require unscheduled visit(s).
b. The participant should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. In case the rash evolves to a higher grade than that first observed, management of the rash should follow the guidelines indicated for the higher grade.
c. If applicable, dermatologist visit should occur preferably within 24 hours after onset of rash.
d. Digital pictures to be taken at the study site.

Notes:

Local laboratory assessments are to be used for rash management. A copy of the local laboratory reports should be de-identified and will be collected by the site manager.

A copy of the dermatologist's report, and biopsy if performed, should be made anonymous and will be collected by the site manager. Dermatologist fees for evaluating participants who experience a rash will be reimbursed by the sponsor.

Digital pictures will be de-identified and stored on the sponsor's secure server. Only the sponsor team members will have access to the sponsor's secure server.

Per investigator's discretion, the participant may be treated symptomatically until the rash resolves.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 5 (28 February 2022)

Overall Rationale for the Amendment: CCI [redacted]

In addition, CCI [redacted] to increase the upper age limit to 60 years of age, to relax the restrictions on the use of CYP3A4 and UGT1A9 inhibitors, to remove the restrictions on the use of substrates for CYP2C9 or CYP2C19, to reschedule the interim analysis at the originally planned time point and to add a primary analysis.

Some minor corrections and/or clarifications were addressed as outlined in the table below.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 5.3.1 Meals and Dietary Restrictions 6.1 Study Intervention(s) Administered	CCI [redacted]	To facilitate cultural and operational aspects of the study and to protect the safety of the participants.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 5. Study Population 5.1 Inclusion Criteria 6.1 Study Intervention(s) Administered 6.3 Measures to Minimize Bias: Randomization and Blinding	The time window of 12 hours between signing ICF and receiving the first dose of study intervention has been removed. Following criteria have been added: • Participants must be identified and screened within 48 hours after onset of fever. • CCI [redacted]	To accommodate the investigator's request.
1.1 Synopsis 4.1 Overall Design 5.1 Inclusion Criteria	The upper age limit for inclusion in the study has been increased to 60 years of age.	To accommodate the investigator's request to be able to include older patients.
2.2 Background 5.2 Exclusion Criteria 6.5 Concomitant Therapy	The restriction on the use of CYP3A4 and UGT1A9 inhibitors has been relaxed to 'within 7 days before first dose of study drug'. Restrictions on the use of substrates for CYP2C9 or CYP2C19 have been removed.	Based on available clinical drug-drug interaction study data, restrictions on concomitant medications have been relaxed.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 8. Study Assessments and Procedures 8.2.1 Physical Examinations 9.4.4 Immune Analysis	The SoA has been updated: • Physical examination during inpatient stay will occur only at screening, Day 3 and Day 6. On the other dosing days, physical examination will be performed ad hoc at the discretion of the principal investigator. Physical examination during the follow-up visits (Days 14, 21, and 28) remains as is. • A clinical status check prior to the first dosing has been added. • Safety laboratory tests have been added on Day 6, at the discretion of the investigator. The blood volume that needs to be collected for the safety laboratory tests as well as the total blood volume for the study have been updated.	To monitor the safety of the study participants.
1.1 Synopsis 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.4.1 General Considerations 9.5 Interim Analysis	The section 'Interim Analysis' has been updated to reschedule the interim analysis at the originally planned time point when at least 50 participants with a primary dengue infection reached Day 28 or discontinued earlier. A primary analysis has been added at the time point when all participants reached Day 28 or discontinued earlier. During this interim and primary analyses, the database will remain blinded to the site personnel to ensure that the 6-months safety follow-up can be performed in a blinded fashion.	The time point of the interim analysis has been rescheduled to the originally planned time point when at least 50 participants with a primary dengue infection reached Day 28 or discontinued earlier. A primary analysis has been added to provide the originally planned 'final analysis' when all participants reached Day 28 or discontinued earlier.
10.7 Appendix 7: Rash Management	The 'Rash Management' appendix has been updated to ensure that only if causal relationship is considered, a rash management should be started. The Day 7 visit and assessments in case of Grade 1 rash have been removed.	Majority of participants will present with a typical dengue-related rash to requiring initiation of the rash management. From safety perspective and to facilitate operational conduct of the study, duration to follow-up Grade 1 rash was reduced.
1.3 Schedule of Activities	The blood sample collection for cellular immunity (PBMC) has been made optional at Day 28.	To accommodate the investigator's request to reduce the total blood volume at Day 28.
1.1 Synopsis 3. Objectives and Endpoints	Two exploratory objectives have been updated: • Investigate the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV RNA in secondary DENV infections and in all DENV infections • Investigate the antiviral activity of JNJ-64281802 versus placebo based on viremia in secondary DENV infections and in all DENV infections	Clarification of the objectives.
9.4.5 Pharmacokinetic Analyses	Additional wording was added to ensure that PK samples collected before a certain date will be included in a population PK analysis.	To analyze the PK profile early in the study.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 6.1 Study Intervention(s) Administered	CCI [redacted]	Correction.
2.2 Background	The clinical background section has been updated to include studies DNG1006 (food effect), DNG1004 (drug-drug interaction) and DNG1005 (drug-drug interaction).	For completeness.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 4.4 End of Study Definition	It has been clarified that participants will be followed up remotely until 6 months after the first dose of study intervention.	Clarification of total study duration.
1.3 Schedule of Activities	It has been clarified that the time window for the study assessments is ±30 min for the assessments at Days 1 to 3 and ±2 hours for the assessments at Days 4 and 5.	For completeness.
8.3.5 Pregnancy	The wording 'and any postnatal sequelae in the infant' has been removed from the below sentence: Follow-up information regarding the outcome of the pregnancy ~~and any postnatal sequelae in the infant~~ will be required.	Correction. The Sponsor follows-up on pregnancy through birth and status of newborn, but no additional follow-up is required, unless safety issues are reported.
Throughout the protocol	Minor updates, corrections, or additions have been made.	Correction, clarification, and consistency.

Amendment 4 (22 November 2021)

Overall Rationale for the Amendment: The protocol was amended to reflect new strategies to expedite participant enrollment, to disallow the use of UGT1A9 inhibitors or inducers before and during the study, to accommodate COVID-19 vaccination strategies, and to extend the follow-up period until 6 months post dosing. In addition, some minor corrections and/or clarifications were addressed as outlined in the table below.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 5.1 Inclusion Criteria 10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Individuals with a suspected dengue virus infection will be asked to undergo an NS1 rapid test under a pre-screening consent during an ambulatory visit organized by the mobile clinical team. Patients who test positive for dengue virus infection will be subsequently referred to the study site.	A broader and more pro-active strategy for participant recruitment will be implemented in order to expedite study enrollment.
5.2 Exclusion Criteria 6.5 Concomitant Therapy	The use of UGT1A9 inhibitors or inducers within 14 days before the first dose of study drug is not permitted.	JNJ-64281802 is a substrate for UGT1A9 based on in vitro results. A possible drug-drug interaction cannot be excluded at this time.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 2.3.4 Potential Risks 5.2 Exclusion Criteria 6.5 Concomitant Therapy 10.9 Appendix 9: COVID-19 Appendix	An authorized/licensed COVID-19 vaccine can be administered at any time before, during, or after the study. COVID-19 testing can be added as a screening assessment at the discretion of the investigator, depending on the epidemiological situation. The COVID-19 appendix has been updated and aligned with other dengue clinical study protocols. Other concomitant vaccinations are not allowed until 30 days after the last dose of study drug, where the period was reduced from 90 to 30 days.	To accommodate COVID-19 vaccination strategies and for alignment within the dengue study program. No substantial accumulation of the compound is expected in the treatment study.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 4.4 End of Study Definition 7.1 Discontinuation of Study Intervention 8.2.1 Physical Examinations 9.4.4.2 Cellular Immune Analyses	Remote every-2-weeks follow-up visits until 6 months after the last dosing day have been added to inquire on any dengue-related signs and symptoms. A distinction between on site (ie, on Days 14, 21, and 28) and remote (ie, every-2-weeks after Day 28 and until 6 months after the last dosing day) follow-up visits was made. As a result, participants will only have completed the study after the final remote follow-up assessment at Mont 6 post dosing.	To accommodate the investigator's request for a longer follow-up period.
1.1 Synopsis 1.3 Schedule of Activities 8.3.2 Method of Detecting Adverse Events and Serious Adverse Events 10.2 Appendix 2: Clinical Laboratory Tests	International normalized ratio (INR) has been specified as an additional parameter in blood coagulation assessments.	The INR is an international standard for the prothrombin time (PT).
1.1 Synopsis 1.3 Schedule of Activities 1.2 Schema 4.1 Overall Design	For eligibility and screening assessments, participants will be directed to the study site. During the treatment phase, participants will be admitted to an inpatient facility. Participants with symptoms of severe dengue or with dengue warning symptoms, will be transferred to a hospital.	To accommodate the site's request to allow for flexibility on where the participant will be admitted. To allow for flexibility on where the participant will be hospitalized.
1.3 Schedule of Activities 8 STUDY ASSESSMENTS AND PROCEDURES	It was emphasized that for all assessments the 30-minute time window as defined in the schedule of activities should be adhered to.	Clarification requested by the study site.
8 STUDY ASSESSMENTS AND PROCEDURES	The blood volume that needs to be collected for each of the assessments has been updated.	For alignment and consistency with laboratory manual and on-site practices.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 8 STUDY ASSESSMENTS AND PROCEDURES 8.1 Antiviral activity Assessments	Samples that tested positive for NS1 rapid test will no longer have to be confirmed by a qualitative PCR at screening.	To expedite screening assessments and start of treatment.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 6.1 Study Intervention(s) Administered	CCI	Clarification requested by the study site.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design	It was emphasized that participants with signs and symptoms of severe dengue can be transferred to a hospital at any time during the study and at the investigator's discretion. Participants with severe dengue OR dengue warning symptoms after Study Day 9 will also be moved to a hospital.	Clarification requested by the study site.
1.1 Synopsis 9.4.2 Antiviral Activity Analysis	Viral load assay results below the limit of detection (LOD) will be described as target not detected.	To align with the data transfer agreement.
1.3 Schedule of Activities	Review of concomitant medication and adverse events were indicated as 'continuously' in the Schedule of Activities.	Clarification as these are being reported on occurrence.
1.1 Synopsis 1.3 Schedule of Activities 2.2 Background 4.1 Overall Design 5.3.1 Meals and Dietary Restrictions 6.1 Study Intervention(s) Administered	CCI	Correction and clarification.
1.3 Schedule of Activities 5.2 Exclusion Criteria 8.2.2 Vital Signs	Oxygen saturation has been removed as a screening assessment and will be measured pre-dose on Day 1 (vital signs).	Correction, clarification, and consistency.
10.2 Appendix 2: Clinical Laboratory Tests	Indirect bilirubin has been removed from the safety laboratory assessments.	Local laboratory cannot provide this test.
8.3.5 Pregnancy	Participants becoming pregnant during the study will discontinue study intervention but will continue study visits for additional safety follow-up.	Correction, clarification, and consistency.
1.3 Schedule of Activities	One line for blood sample collection for NS1 concentration was removed from the schedule of activities.	Correction, as the assessment was duplicated.
10.7 Appendix 7: Rash Management	The word 'asymptomatic' has been removed to describe a Grade 1 rash.	To align wording across studies.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design	Screening and baseline assessments are completed on Day 0.	Correction to align with the Schedule of Activities.
Throughout the protocol	Minor updates, corrections, or additions have been made.	Correction, clarification, and consistency.

Amendment 3 (26 March 2021)

Overall Rationale for the Amendment: The protocol was amended as specified below.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 2.2 Background 4.1 Overall Design 5.3.1 Meals and Dietary Restrictions 6.1 Study Intervention(s) Administered	CCI	To facilitate cultural and operational aspects of the study.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design	CCI	To offer additional guidance to the study site.
1.3 Schedule of Activities	Guidance on the allowed blood sampling time window was added to the schedule of activities.	To offer additional guidance to the study site.
1.1 Synopsis 4.1 Overall Design 9.5 Interim Analysis	Sentence was added with regards to treatment effect and the futility stopping boundary at the time of the interim analysis.	To get a better understanding of how different the observed versus the assumed effect can be, in order to make a well-informed sponsor decision at the time of the interim analysis.
1.1 Synopsis 5.1 Inclusion Criteria 7.2.1 Withdrawal from the Use of Research Samples 8 STUDY ASSESSMENTS AND PROCEDURES 8.6.1 Human Leucocyte Antigen Typing and Pharmacogenomics Assessments 10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Because human leukocyte antigen (HLA) and pharmacogenomic samples are required, the word 'optional' was removed. Where local regulations require, a separate consent can be obtained for this part of the study. The use of leftover samples for future exploratory research is optional and will be consented separately in the informed consent form (ICF).	Clarification and correction of inconsistencies.
2.2 Background 2.3.4 Potential Risks	Information on cardiovascular safety was removed from potential risks. Instead, a paragraph on exposure analysis was added to the overall safety data.	Cardiovascular safety is not considered to be a potential risk.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.2.2 Vital Signs	Input-Output (I/O) ratio will be measured from predose till discharge, not during screening.	Correction of errors and inconsistencies.
1.1 Synopsis 1.2 Schema 4.1 Overall Design 10.1 Appendix 1: Abbreviations	Participants with severe dengue after Day 9 will be transferred to the Singapore General Hospital (SGH), and not to the National University Hospital. In addition, at the investigator's discretion, participants who are hemodynamically unstable or require interventions, can be transferred to the SGH anytime during the inpatient stay at the investigational medicine unit (IMU).	Updates made based on site-specific input.
1.2 Schema 1.3 Schedule of Activities 10.9 Appendix 9: COVID-19 Appendix	Hospitalization at the SingHealth investigational medicine unit (IMU) has been replaced with inpatient stay at IMU.	Update in terminology to make a clear distinction between inpatient stay at IMU during treatment and transfer to the hospital for participants with severe dengue.
1.1 Synopsis 4.1 Overall Design 5.1 Inclusion Criteria 10.1 Appendix 1: Abbreviations	The terminology healthcare clinics (HCCs) was changed to general practitioner clinics (GP) throughout the document.	Correction of errors and inconsistencies.
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events	Anticipated events and Anticipated Events Safety Monitoring Plan were removed, because they are not applicable for this study.	Correction of errors and inconsistencies.
8.5.3 Pharmacokinetic Parameters and Evaluations	Plasma protein binding was replaced with 'protein binding' with regards to Alpha-1 acid glycoprotein, because this is detected in serum not plasma.	Correction of errors and inconsistencies.
10.2 Appendix 2: Clinical Laboratory Tests	C-reactive protein was added to the biochemistry assessments.	Clarification.
4.1 Overall Design 10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	It was clarified that the data review committee (DRC) will be consulted in case of significant or unexpected safety events and for quarterly (or when 50 new participants are enrolled, whichever comes first) safety analyses.	Clarification.
2.3.4 Potential Risks 5.2 Exclusion Criteria 6.5 Concomitant Therapy	COVID-19 vaccination was added as an exception to be allowed as concomitant vaccination 30 days after the last dosing.	To accommodate for COVID-19 vaccinations during the pandemic.
1.1 Synopsis 4.1 Overall Design	Follow-up period has been corrected to 23 days (±2 days) after the last dosing day.	Alignment with the SoA.
1.1 Synopsis 4.1 Overall Design	CCI [redacted]	Alignment with the SoA.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 6.1 Study Intervention(s) Administered 6.3 Measures to Minimize Bias: Randomization and Blinding	CCI [redacted]	Alignment within the protocol.
10.7 Appendix 7: Rash Management	The updated rash management section has been added to this protocol.	Alignment between studies.
8.1 Antiviral activity Assessments 8.2.4 Clinical Safety Laboratory Assessments 8.6 Genetics	Paragraphs on viral genome sequencing and clinical endpoint assessments have been moved to the correct and corresponding subsection.	Correction.
Throughout the protocol	Minor updates, corrections, or additions have been made.	Correction, clarification, and consistency.

Amendment 2 (08 September 2020)

Overall Rationale for the Amendment: The protocol was amended to incorporate changes related to the new study drug formulation and as specified below.

Section number and Name	Description of Change	Brief Rationale
10.9 Appendix 9: COVID-19 Appendix	A COVID-19 appendix was added.	To provide guidance on study conduct during the COVID-19 pandemic.
8.2.1 Physical Examinations	Body weight recording and physical examinations were aligned with the Schedule of Activities.	To maintain consistency throughout the protocol.
8 Study Assessments and Procedures	The total blood volume for the study was decreased with 5 mL to approximately 382 mL for males and 384.5 mL for females.	Serology for HIV and Hepatitis was removed from screening in the previous amendment without adjusting the total blood volume to be drawn.
Throughout the protocol	Minor updates, corrections, or additions have been made.	Correction, clarification, and consistency.

Amendment 1 (4 August 2020)

Overall Rationale for the Amendment: The protocol was amended to incorporate changes related to the new study drug formulation and as specified below.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.1 Study Intervention(s) Administered	CCI [redacted]	This formulation was selected based on the findings from the 64281802DNG1001 study.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 2.2 Background 4.1 Overall Design 5.3.1 Meals and Dietary Restrictions 6.1 Study Intervention(s) Administered	CCI [redacted]	This is a result of the changed study drug formulation.
6.5 Concomitant Therapy	The use of loperamide was restricted to a period of maximum 3 consecutive days.	No maximum duration of loperamide use was formulated.
1.3 Schedule of Activities 8 Study Assessments and Procedures 10.2 Appendix 2: Clinical Laboratory Tests	Serology for HIV and Hepatitis has been removed from screening.	HIV and Hepatitis are no inclusion/exclusion criteria. Results from baseline testing might not be received in time and will not alter eligibility or dosing.
5.1 Inclusion Criteria	Chromosomal complement to determine sex has been removed.	Chromosomal complement testing is not available.
5.2 Exclusion Criteria 5.3.3 Activity	No blood donation within 90 days after last dose of study intervention.	To maintain consistency throughout and across protocol(s).
5.3.3 Activity	No participation in other investigational studies within 90 days of the last dose of study drug intake.	To maintain consistency across the protocol (exclusion criterion 9).
2.3.4 Potential Risks	Vaccinations are not allowed until 90 days after the last dose of study drug intake.	To maintain consistency across protocols.
2.1 Study Rationale	The number of reported dengue cases has been updated to the date of this amendment.	To provide accurate and contemporaneous data.

10.9. Appendix 9: COVID-19 Appendix

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; lock-down situations imposed by (local) governments; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks; and courier/shipment restrictions.

In alignment with recent Health Authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements nor the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key endpoint assessments related to treatment outcomes should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirements.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via the COVID-19 appendix after consultation with the participants, investigator, and the sponsor. Missed or modified assessments/visits, discontinuations of study intervention, and withdrawal from the study due to COVID-19-related circumstances, should be documented as protocol deviations with the prefix "COVID-19-related" in the electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the relevant Health Authorities/Ethics Committees according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical monitor to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

The following provisions are meant to give guidance and mitigations for impacted study conduct due to COVID-19 pandemic in order to warrant the participant's safety and data collection/quality.

Clinical Aspects

Participants

As for any other comorbidity, the investigator needs to diagnose and treat any (suspected) COVID-19 disease per standard-of-care and per local/national guidance.

If a participant, in any phase of this study, becomes symptomatic for COVID-19 disease, the sponsor suggests that the coronavirus infection should be confirmed by using locally approved

laboratory test kits, eg, a diagnostic kit using RT-PCR. This should be reported to the local Health Authorities as required.

The investigator needs to evaluate and discuss with the sponsor's medical monitor when a participant develops acute COVID-19 during the study. This should be reported as an Adverse Event (AE). Withdrawal from the study due to an AE of suspected or confirmed SARS-CoV-2 infection in a participant should be documented as discontinuation due to an AE in the eCRF.

The investigator should notify the sponsor's medical monitor as soon as he/she is aware of a suspected or confirmed SARS-CoV-2 infection in a participant.

The investigator should notify the treating physician of the participant's participation in the study and details of the study.

Site Staff

The investigator is to follow any local or government requirements and exercise his or her clinical judgement to protect the health and well-being of participants, and site staff.

Visits/Assessments

If a participant cannot visit the study site in person for the protocol-required assessments, or if certain assessments cannot be performed (as usual), or if there are transport restrictions for samples, the site staff/investigator should discuss with the sponsor how the participant's safety and data collection/quality is guaranteed as much as possible.

- In case visits to the study site are not possible, mitigations include: remote contacts, phone contacts, or delay of the visit if acceptable based on the investigator's clinical judgement and approval by the sponsor.
- In case assessments cannot be performed per protocol at the study site, alternatives may be possible after discussion and agreement with the sponsor.

  There are some assessments that could be conducted remotely via telephone (or videoconference) with participants confined at home. This methodology can only be used in accordance with applicable (including local) laws, regulations, guidance, and procedures. These remote assessments include review of AEs and concomitant medications. It must be documented in the participant's source documents and eCRF if a visit occurs remotely due to COVID-19.

  If due to local or national guidance or regulations, for safety reasons of the participants or site staff or to avoid spread of coronavirus infection, certain assessments cannot be performed or are to be performed differently, this is to be documented in the source documents and the eCRF.
- In case transportation to the central laboratory is not possible, the PK blood samples should be stored at -20°C until transportation of the sample is possible.

If a participant's safety and/or data collection and integrity are not guaranteed, it may be decided to interrupt/stop the participant follow-up as per Section 7 in the protocol.

Study Drug

Drug administration will be discontinued when participants are not in the ability to come to the study site (no home dosing).

Missed or Modified Assessments/Protocol Deviations

Missed or modified assessments/visits will be captured in the Electronic Data Capture (EDC) as protocol deviations with the prefix "COVID-19-related".

In case of any protocol deviation due to COVID-19 (eg, remote visits, missed or modified assessments/visits, and out of window visits), it is recommended that these would be captured in the participant's source documents by the site personnel with the prefix "COVID-19-related".

Monitoring/Audits/Consent/Ethics

On-site Monitoring visits

In case on-site monitoring visits are not possible due to local regulations, restrictions, and guidance, the site monitor may conduct certain monitoring activities remotely. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Audits

To comply with national, local, and/or organizational social distancing restrictions due to COVID-19, study-site Good Clinical Practices (GCP) Audits with direct impact/engagement from the clinical investigator team may not be conducted at the impacted sites. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.

Consent

In case any required assessments cannot be performed per protocol due to COVID-19, the investigator should inform the participant about the changes and document the discussion in the participant's source notes.

Ethics

In case of any protocol deviations related to COVID-19, the investigator should notify these to the local Ethics Committees/Health Authorities per local requirements.

Study Conduct Related to COVID-19 Vaccine Deployment for Non-COVID-19 Clinical Trials

- An authorized/licensed COVID-19 vaccine will be allowed at any time before, during, and after the study. The COVID-19 vaccine will be reported as a concomitant medication.
- Side effects of vaccination will be reported as AEs, defining the causality of AEs will rely on the medical judgement of the principal investigator of the study.

- SUSAR reporting must be initiated if the serious adverse reaction is unexpected.
- If the event is serious and considered related to both the COVID-19 vaccine and the study intervention, it has to be recorded as a serious adverse reaction.

11. REFERENCES

American Red Cross. Blood needs & blood supply. http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics 2020. Accessed 3 March 2020.

Ben-Shachar R, Koelle K. 2015 Minimal within-host dengue models highlight the specific roles of the immune response in primary and secondary dengue infections. J. R. Soc. Interface 2015;12(103): pii:20140886.

Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-507.

Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infections in Bangkok. Am J Trop Med Hyg. 1988;38:172–80.

Carrington LB, Simmons CP. Human to mosquito transmission of dengue viruses. Front Immunol. 2014; 5:290.

Centers for Disease Control and Prevention. Dengue statistics and maps. 2020. Available at: https://www.cdc.gov/dengue/statistics-maps/index.html (accessed 12 February 2020)

Clapham HE, Cummings DAT, Johansson MA. Immune status alters the probability of apparent illness due to dengue virus infection: Evidence from a pooled analysis across multiple cohort and cluster studies. PLoS Negl Trop Dis. 2017;11(9):e0005926.

Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. 1998;11(3):480-496.

Gubler DJ. Dengue, urbanization and globalization: The unholy trinity of the 21(st) century. Trop Med Health. 2011;39(4 Suppl):3-11.

Guzman MG, Vazquez S. The complexity of antibody-dependent enhancement of dengue virus infection. Viruses. 2010;2(12):2649-2662.

Huang HW, Tseng HC, Lee CH, Chuang HY, Lin SH. Clinical significance of skin rash in dengue fever: A focus on discomfort, complications, and disease outcome. Asian Pac. J. Trop. Med. 2016;9(7):713-718.

Investigator's Brochure: JNJ-64281802. Edition 2. Janssen Research & Development (November 2019).

Investigator’s Brochure Addendum to Edition 2: JNJ-64281802. Janssen Research & Development (January 2020).

Jenny G Low, Cynthia Sung, Limin Wijaya, 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.

Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clin Epidemiol. 2013; 5:299-309.

National Environment Agency. Dengue Cases. Available at: https://www.nea.gov.sg/dengue-zika/dengue/dengue-cases. 2020. Accessed 31 July 2020.

Nguyet Minh Nguyen, Chau Nguyen Bich Tran, Lam Khanh Phung, et al. A randomized, double-blind placebo controlled trial of balapiravir, a polymerase inhibitor, in adult dengue patients. 207(9), 1442-1450.

Poggio, ED, Wang, X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and cockcroft-gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephr. 2005; 16:459-466.

Rodriguez F, Harrison RW, Wojdyla D, Mahaffey KW. Lost to follow-up and withdrawal of consent in contemporary global cardiovascular randomized clinical trials. Crit Pathways in Cardiol. 2015;14:150-153.

Shepard D, Undurraga E, Halasa Y, Stanaway J. The global economic burden of dengue: a systematic analysis. Lancet Inf Dis. 2016; 16:935–41.

Tricou V, Minh NN, Farrar J, Tran HT, Simmons CP. Kinetics of viremia and NS1 antigenemia are shaped by immune status and virus serotype in adults with dengue. PLoS Negl Trop Dis. 2011;5(9).

Whitehorn J, Simmons CP. The pathogenesis of dengue. Vaccine. 2011;29(42):7221-7228.

World Health Organization. Guidelines for plaque reduction neutralization testing of human antibodies to dengue viruses. 2007

World Health Organization. A joint publication of the World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases (TDR). Dengue guidelines for diagnosis, treatment, prevention and control. New edition. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf?ua=1. 2009. Accessed 03 May 2018.

World Health Organization: Dengue. Guidelines for diagnosis, treatment, prevention and control. 2009

World Health Organization. Dengue and severe dengue. WHO website. http://www.who.int/mediacentre/factsheets/fs117/en/. Updated November 2019. Accessed 07 November 2019.

World Health Organization. Ten threats to global health in 2019. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019. 2019. Accessed 07 November 2019.

Xie X, Zou J, Wang QY, Shi PY. Targeting dengue virus NS4B protein for drug discovery. Antiviral Res. 2015; 118:39-45.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed):

Institution and Address:

Telephone Number:

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: Electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	07-Jun-2022 01:13:41 (GMT)	Document Approval