Janssen Research & Development *

Clinical Protocol

Protocol Title
A Phase 2, Randomized, Double-blind, Placebo-controlled, Double-dummy, Multicenter Trial Assessing the Efficacy and Safety of Two Dose Regimens of JNJ-64281802 for the Prevention of Dengue Infection.

Protocol 64281802DNG2004; Phase 2
AMENDMENT 3

JNJ-64281802

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

IND: 143525

Status: Approved
Date: 19 July 2023
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-145705, 4.0

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 3	18 July 2023
Amendment 2	02 December 2022
Amendment 1	04 October 2022
Original Protocol	09 November 2021

Amendment 3 (18 July 2023)

Overall Rationale for the Amendment: The main purpose of this amendment is to clarify and simplify some operational aspects of the study, to avoid potential confusion or misinterpretation, and to facilitate study conduct.

Clarifications were provided with regards to the timing of study intervention dosing and the term household contact (HHC). Updates were made to some inclusion and exclusion criteria, the discontinuation criteria, and the lists of allowed and disallowed concomitant therapy and contraceptives. The US FDA toxicity grading Table was replaced with information obtained from the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events and supplemented with WHO toxicity grading scales where values were absent, and further clarifications and corrections were made. The changes made to the clinical protocol 64281802DNG2004 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in the previous protocol amendments are listed in Section 10.12Appendix 12: Protocol Amendment History.

Section number and Name	Description of Change	Brief Rationale
Synopsis 1.3.2.2 Double-blind Prophylactic Dosing of HHCs: Day 1 to Day 13 1.3.2.3 Double-blind Prophylactic Dosing of HHCs (Day 14 to Day 28) and Follow-up Phase4.1 Overall Design 6.1 Study Intervention(s) Administered 6.4 Study Intervention Compliance 8 STUDY ASSESSMENTS AND PROCEDURES	The timing of the loading dose and maintenance dose administrations was clarified.	For clarification.
Synopsis 4.1 Overall Design 5 STUDY POPULATION	It was clarified that HHCs may include family members, acquaintances, co-workers, and community contacts of the index case.	For clarification.
5.1 Inclusion Criteria	It was clarified that abnormal blood pressure results are only exclusionary for HHCs if the investigator judges the deviations from normal blood pressure are clinically significant.	For clarification.
5.2 Exclusion Criteria	It was clarified that clinically relevant skin diseases are exclusionary for HHCs if the clinically relevant skin disease	To allow enrollment of participants with any clinically relevant skin disease ≥ 3 months prior to enrollment, instead of ≥ 5 years.

Section number and Name	Description of Change	Brief Rationale
	occurred within 3 months prior to study enrollment.	
5.2 Exclusion Criteria	It was clarified that prior treatment with immunomodulation therapy is exclusionary for HHCs if the therapy was taken within the past 6 months.	To allow enrollment of participants with a history of immunomodulatory therapy ≥ 6 months prior to enrollment.
5.2 Exclusion Criteria	It was clarified that prior receipt of an investigational intervention or prior use of an invasive investigational medical device is exclusionary for HHCs if the investigational intervention or invasive investigational medical device was used within 3 months before the planned first dose of study intervention.	To allow enrollment of participants with a history of using investigational intervention or invasive investigational medical device products ≥3 months prior to enrollment.
2.3.1 Risks for Study Participation 5.2 Exclusion Criteria 6.8 Concomitant Therapy 10.4 Appendix 4: COVID-19 Appendix	Participants will be allowed to receive a COVID-19 vaccine during the study.	To allow participants to receive a COVID-19 vaccine and adhere to national/local vaccination recommendations.
5.2 Exclusion Criteria 6.8 Concomitant Therapy 10.10 Appendix 10: Examples of Disallowed Medications	The concomitant use of CYP3A4 inhibitors, inducers, and substrates, as well as BCRP substrates, was clarified. CYP3A4 substrates were limited to those with narrow therapeutic index, and CYP3A4 inhibitors and CYP3A4 inducers were limited to strong ones. Examples of disallowed medications were provided. In addition, some inconsistencies between Exclusion Criterion 11 and the concomitant therapy section were corrected.	JNJ-64281802 is a weak inhibitor of CYPs 2C8, 2C9, 2C19, and 3A4 based on a cocktail drug interaction study (64281802DNG1004) using repaglinide, warfarin, omeprazole, and midazolam respectively as probes. Substrates of CYP2C8, 2C9, and 2C19 do not warrant exclusion but should be appropriately monitored if coadministered.
5.2 Exclusion Criteria	It was specified that the medical history of participants should be evaluated based on clinical significance by the investigator.	For clarification.
5.2 Exclusion Criteria 6.8 Concomitant Therapy	A change was made in the time period for administration of licensed (not live) vaccines.	To facilitate participant enrollment and for clarification.
6.8 Concomitant Therapy	Details regarding the use of paracetamol/acetaminophen were added.	To broaden the use of co-medication and to add more detailed instructions regarding their use.
5.1 Inclusion Criteria 10.5 Appendix 5: Contraceptive and Barrier Guidance	It was clarified that the use of estrogen and/or progestogen hormonal contraception is not	The interaction between JNJ-64281802 and hormone-based contraceptives has not been assessed. The efficacy of hormone-based

Section number and Name	Description of Change	Brief Rationale
	allowed as sole method of contraception during the study.	contraceptives may be decreased when coadministered with JNJ-64281802 and therefore should not be considered a highly effective contraceptive method during dosing with JNJ-64281802. A woman using any type of hormonal contraception must use an additional barrier-based contraceptive method.
7.1 Discontinuation of Study Intervention	Discontinuation criteria based on laboratory abnormalities were updated.	To accommodate laboratory values that can be expected in the diverse population included in this global study and that are not anticipated to pose a safety risk.
8.3.2 Method of Detecting Adverse Events and Serious Adverse Events	Laboratory events were removed from the list of solicited AEs.	Since laboratory assessments are an objective measurement, it is incorrect to categorize them as solicited AEs. Solicited AEs are predefined events for which the participant is specifically questioned.
1.3.2.2 Double-blind Prophylactic Dosing of HHCs: Day 1 to Day 13 1.3.2.3 Double-blind Prophylactic Dosing of HHCs (Day 14 to Day 28) and Follow-up Phase 1.3.2.4 Discontinuation From Study Intervention or Study 8 STUDY ASSESSMENTS AND PROCEDURES 10.8 Appendix 8: Clinical Laboratory Tests	It was clarified that baseline laboratory assessments for clinical chemistry and coagulation should, in addition to being performed centrally, be performed locally. Local testing at subsequent visits is at the discretion of the PI and if requested by the Sponsor.	To facilitate evaluation and monitoring of participant safety regarding discontinuation criteria in a timelier manner at baseline.
Synopsis 8.3.2 Method of Detecting Adverse Events and Serious Adverse Events 9.4.4.1 Safety Analyses 10.7.3 Severity Criteria 10.9 Appendix 9: Toxicity Grading Scale for Determining the Severity of Adverse Events	The US FDA toxicity grading Table was replaced with information obtained from the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events and supplemented with WHO toxicity grading scales where values were absent.	The DAIDS Toxicity Grading Scale supplemented with WHO toxicity grading scales was considered more appropriate, given the global nature of this study, including a diverse population.
1.3.2.4 Discontinuation From Study Intervention or Study 8.2.5 Pregnancy Testing 10.8 Appendix 8: Clinical Laboratory Tests	It was clarified that a pregnancy test will be performed at screening, on Days 28 and 50, and during a withdrawal visit, and that additional pregnancy tests may be performed as determined necessary by the investigator or required by local regulations.	To correct an inconsistency.
5.4 Screen Failures	It was clarified that the investigator will not generate screening and enrollment logs.	To align with the company's most recent protocol template per company policy.
7.1.2 Participant Stopping Criteria due to Liver Chemistry	Liver chemistry stopping criteria were added.	To provide guidelines for actions required for participants who develop

Section number and Name	Description of Change	Brief Rationale
10.11 Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments		ALT and AST elevations during the participation of the study.
1.1 Synopsis 1.3.1 Index Cases 4.1 Overall Design 5.1 Inclusion Criteria 8.1.1.1 Antiviral Activity 8.7.1 NS1 Test and RT-PCR/anti-DENV IgM test of Index Cases	Removal of 'rapid' test.	To not restrict inclusion based on diagnostic test.
1.1 Synopsis 4.1 Overall Design	Informed consent from ICs may be obtained remotely.	For clarification.
1.1 Synopsis 4.1 Overall Design	Confirmation of baseline DENV infection is to be performed at a central laboratory.	For clarification.
1.1 Synopsis 1.3.2.1 Screening Phase 1.3.2.2 Double-blind Prophylactic Dosing of HHCs: Day 1 to Day 13 1.3.2.3 Double-blind Prophylactic Dosing of HHCs (Day 14 to Day 28) and Follow-up Phase 1.3.2.4 Discontinuation From Study Intervention or Study 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.2 Vital Signs 8.3.2 Method of Detecting Adverse Events and Serious Adverse Events 10.3 Appendix 3: WHO Clinical Classification of Dengue Disease	Measurement of body temperature should be performed orally. No antipyretic medications are allowed prior to body temperature measurement for at least 4 hours.	For clarification.
1.3.1 Index Cases	It was added that AEs related to blood sampling from ICs will be collected.	To include the need to report AEs related to blood sampling.
Throughout the protocol	Minor grammatical, formatting, or spelling changes and clarifications were made.	Minor errors were corrected.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2, Randomized, Double-blind, Placebo-controlled, Double-dummy, Multicenter Trial Assessing the Efficacy and Safety of Two Dose Regimens of JNJ-64281802 for the Prevention of Dengue Infection.

JNJ-64281802 is a novel antidengue virus (DENV) small molecule targeting DENV nonstructural protein (NS)4B. It has shown potent antiviral activity against all 4 DENV serotypes in nonclinical studies. By disrupting the DENV viral replication, JNJ-64281802 could potentially reduce the viral load (VL) and/or prevent viremia from emerging and thereby reduce or even prevent DENV infection-associated morbidity and mortality.

This study has 4 sequential phases: DENV-infected index case identification, screening of the household contacts (HHCs) which may include family members, acquaintances, co-workers, and community contacts of the index case, double-blind prophylactic dosing of HHCs, and follow-up phases.

This study will include index cases ≥1 years of age who will participate for one visit only and HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years who are eligible to be included in the intervention part of the study. HHCs must not have DENV-associated clinical signs and symptoms at baseline.

"Participant" refers to HHCs, unless index cases are explicitly mentioned. When "participant" is referred to in relation to the informed consent form (ICF), this can be either a HHC or an index case; when "participant" is referred to in relation to the informed assent form, this refers to an index case.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of laboratory-confirmed DENV infection up to the last day of dosing among HHC who have no evidence of current DENV infection at baseline.	• Laboratory-confirmed DENV infection[a] between baseline and the last day of dosing.
Key Secondary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection through development of signs and symptoms up to the last day of dosing (see Safety Evaluations section) among all HHC.	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing.
Secondary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection through development of signs and symptoms up to the last day of dosing (see Safety Evaluations section) among HHC who have no evidence of current DENV infection at baseline.	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing.

Objectives	Endpoints
• To assess the safety and tolerability of 2 dose regimens (high and low) of JNJ-64281802 among HHC.	• Safety and tolerability as measured by recording of adverse events (AEs), serious adverse events (SAEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory assessments.
• To assess the pharmacokinetics (PK) of JNJ-64281802 following repeated oral dosing among HHC.	• PK parameters for JNJ-64281802 (area under the concentration curve during one dosing interval [AUC_{τ}], observed analyte concentration just prior to the beginning or at the end of a dosing interval [C_{trough}], and maximum observed analyte concentration [C_{max}]).
• To assess the relationship between the PK and pharmacodynamics (PD); selected antiviral activity of JNJ-64281802, clinical outcome, and safety parameters) after repeated dosing of JNJ-64281802 among HHC.	• Laboratory-confirmed DENV infection[a] between baseline and the last day of dosing. • PK (plasma concentrations or exposure parameters) of JNJ-64281802. • Safety parameters. • Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing.
Exploratory	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection up to the last day of dosing as measured by DENV ribonucleic acid (RNA) among HHC who have no evidence of current DENV infection at baseline.	• Presence or absence of a positive DENV RNA test result between baseline and the last day of dosing.
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the reduction of DENV RNA among enrolled HHC who have no evidence of current DENV infection at baseline and who are infected post baseline.	• The maximum DENV RNA levels between baseline and last day of dosing.
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection up to the last day of dosing as measured by detection of DENV NS1 protein among HHC who have no evidence of current DENV infection at baseline.	• Presence or absence of a positive DENV NS1 protein test result between baseline and the last day of dosing.
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection as measured by increase in anti-DENV antibodies among HHC who have no evidence of current DENV infection at baseline.	• Increase in anti-DENV antibody between baseline and Day 40. • Increase in anti-DENV antibody between baseline and Day 50. • Increase in anti-DENV antibody between baseline and Day 90.

Objectives	Endpoints
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection up to Day 40, 50, and 90 among all HHC who completed study intervention (28 days).	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and Day 40. • Laboratory-confirmed symptomatic DENV infection[b] between baseline and Day 50. • Laboratory-confirmed symptomatic DENV infection[b] between baseline and Day 90.
• To evaluate the antiviral effect of JNJ-64281802 as early treatment among HHC who have evidence of DENV infection at baseline.	• Time to end of detectable DENV RNA and/or reduction in DENV RNA load. • Time to end of detectable DENV NS1 protein. • DENV-associated signs and symptoms.
• To identify circulating DENV serotypes/genotypes and genetic variants among index cases and HHC.	• Serotype/genotype of DENV based on viral genome sequence analysis. • Genetic variation of viral genome sequence based on changes at the amino acid level • Emergent JNJ-64281802 resistance-associated mutations in HHC using index case sequence as reference.

AE = adverse event; DENV = dengue virus; ECG = electrocardiogram; HHC = household contact; nAb = neutralizing antibody; NS = non-structural protein; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic(s); RNA = ribonucleic acid; SAE = serious adverse event.

[a] Laboratory-confirmed DENV infection is defined as a positive DENV RNA or DENV NS1 protein test result.
[b] Laboratory-confirmed symptomatic DENV infection is defined as having at least 2 solicited systemic AEs (see Safety Evaluations section), of which at least one is a most common dengue symptom (ie, fever, headache/retro-orbital pain, myalgia, arthralgia, rash), lasting for ≥1 day and occurring within a +/-2-day window around the positive PCR or NS1 test, between baseline and the last day of dosing.

HYPOTHESIS

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to prevention of laboratory-confirmed DENV infection between baseline and the last day of dosing in study participants who are DENV RNA and NS1 protein negative at baseline. Laboratory-confirmed DENV infection is defined as a positive DENV RNA and/or DENV NS1 protein test result.

OVERALL DESIGN

This is a Phase 2 randomized, double-blind, placebo-controlled, double-dummy, multicenter, interventional study, assessing the efficacy and safety of 2 dose regimens of JNJ-64281802 for the prevention of dengue infection in HHCs of a DENV-infected index case.

The study will be conducted in approximately 10 countries in South-East Asia and the American continent.

The study has 4 sequential phases: DENV-infected index case identification, screening of the HHCs which may include family members, acquaintances, co-workers, and community contacts of the index case, double-blind prophylactic dosing of HHCs, and follow-up phases.

The study consists of 2 stages, with an interim analysis (IA) planned at the end of Stage 1 and the final analysis (FA) planned at the end of Stage 2 (i.e., at the end of the study). The IA will be performed by an independent statistical support group and will be reviewed by the Independent Data Monitoring Committee (IDMC) who will receive unblinded safety and efficacy data. After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study (see Interim Analysis section). A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making considering the IDMC recommendation. The FA will be performed by the sponsor who will be fully unblinded to the treatment allocation at that time.

This study consists of a main study (see below) and a PK substudy (see Pharmacokinetic Substudy section).

Assessments and visits to the site will be performed as indicated in the Schedule of Activities.

DENV-infected Index Case Identification

An index case is a patient (≥1 years old) with laboratory-confirmed dengue identified in the community (ie, hospital and/or health care center [HCC]/health care provider [HCP]). Laboratory-confirmed dengue for an index case is defined as:

1. Any DENV-associated signs and symptoms ≤72 hours of onset (according to World Health Organization [WHO] clinical classification of dengue disease), AND
2. A positive DENV NS1 test at screening. Results from tests performed as part of the local standard-of-care ≤72 hours of screening can be used for screening for this study. If a DENV NS1 test is not available, a DENV polymerase chain reaction (PCR) test or anti-DENV immunoglobulin M (IgM) test can also be used.

After informed consent/assent is obtained, either at the site or remotely (eg, at the index case's home), a blood sample for viral assessments will be collected, and the person's HHCs will be contacted. If the index case is a minor according to the local laws and regulations, assent and informed consent from the parent(s) or legal guardian(s) or legally acceptable representative(s) will be obtained.

Screening of the Household/Community Contacts of the Index Case

An HHC is a person who lives, spends the night, or regularly attends/shares/consumes cooking/meals in the same dwelling or housing complex as the index case. A household can include one or more families, , or community contacts in a single or in multiple houses or dwellings, depending on the country, site, social-economic, and cultural characteristics. Co-workers and acquaintances can also be considered HHCs, if they spend time together with the index case (eg, during early morning hours or twilight hours).

HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years can be included in the intervention part of the study. HHCs must be asymptomatic at screening and can include participants with no evidence of current DENV infection (consisting of naïve and historical DENV-infected participants) or with evidence of current DENV infection as confirmed by laboratory assessments, performed at a central laboratory on samples taken at baseline (see Section 1.2, Schema).

Screening for eligible HHC(s) will be performed within 48 hours of obtaining informed consent/assent of the index case. For this purpose, HHCs will be invited to the study site. Informed consent of the HHC will be obtained on site or remotely.

Double-blind Prophylactic Dosing of HHCs

Participants will be randomized in a 1:1:1 ratio to receive a high- or low-dose study intervention, or matching placebo in a double-dummy fashion (see table below) for 28 days. The study will use randomization at the individual participant level, stratified by country.

- High-dose JNJ-64281802 regimen (HDR):
  - 400 mg JNJ-64281802 loading dose (LD) twice daily for 48 hours, followed by
  - 150 mg JNJ-64281802 maintenance dose (MD) once daily for 26 days.
- Low-dose JNJ-64281802 regimen (LDR):
  - 150 mg JNJ-64281802 (LD) twice daily for 48 hours, followed by
  - 50 mg JNJ-64281802 (MD) once daily for 26 days.
- Placebo (double-dummy; see table below).

LDs need to be taken twice daily, approximately around the same timepoints. MDs will start after the last LD and need to be taken once daily, approximately around the same timepoint, until Day 28.

The study intervention is to be taken in fed conditions (for details, see table below). Study intervention can be taken with water.

Development of DENV-associated clinical signs and symptoms (according to WHO clinical classification of dengue disease) will be evaluated and recorded, virologic and serologic testing, and safety assessments will be performed.

A PK substudy will be performed (see Pharmacokinetic Substudy section below).

Follow-up Phase

Double-blind prophylactic dosing of HHCs will be followed by intensive follow-up until Day 50 and a last visit on Day 90. At the end-of-study visit, assessments will be performed as indicated in Section 1.3.2.3.

Stopping Criteria

HHCs who develop DENV-associated clinical warning signs and symptoms (according to WHO clinical classification of dengue disease [WHO 2022]) during the study and require hospitalization will be withdrawn from study intervention. The participant will perform a withdrawal and safety follow-up visit as described in Section 1.3.2.4, Discontinuation From Study Intervention or Study.

The participant will receive medical care according to local standards. Hospitalization is classified as SAE and should be reported accordingly.

NUMBER OF PARTICIPANTS

The study is event driven, with a target number of 36 DENV infections observed in HHCs without evidence of DENV infection at baseline (ie, primary study population) and 24 symptomatic DENV infections observed in all HHCs (ie, complete study population). Under the current assumptions, between 1,250 and 1,850 participants are expected to be enrolled in the study.

This study will include index cases ≥1 years of age with laboratory-confirmed dengue infection and HHCs 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age, inclusive, with a body mass index (BMI) between 18.0 and 35.0 kg/m^2 (inclusive), and body weight ≥40.0 kg at screening without DENV signs and symptoms at baseline.

A PK substudy will be performed in 30 to 40 participants (see Pharmacokinetic Substudy section below).

INTERVENTION GROUPS AND DURATION

HHCs will receive the study interventions as described above in the Overall Design section. Total study duration will be approximately 13 weeks for HHCs.

Index case participation in the study will involve only one visit.

DESCRIPTION OF INTERVENTIONS

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Route of Administration	Oral	Oral

Intervention Name	JNJ-64281802	Placebo
Food/Fasting Requirement	The study intervention is to be taken in fed conditions, ie, within 30 minutes after the start of the participant's regular meal (eg, breakfast, lunch, snack, and/or dinner).	The study intervention is to be taken in fed conditions, ie, within 30 minutes after the start of the participant's regular meal (eg, breakfast, lunch, snack, and/or dinner).
Use	Experimental	Placebo

LD = loading dose; MD = maintenance dose.

EFFICACY EVALUATIONS

Virology

Antiviral Activity

Antiviral activity will be assessed by measuring DENV RNA levels and DENV NS1 protein levels in serum of the HHCs. Serum DENV RNA levels will be assessed using a validated quantitative DENV reverse transcription PCR (RT-qPCR) assay and serum DENV NS1 protein levels will be assessed using an ELISA-based assay.

Viral Genome Sequencing and Dengue Virus Serotyping

Blood sampling for viral genome sequence analysis on index cases and HHCs will be performed. Viral sequencing will only be performed on DENV RNA positive samples at the discretion of the sponsor's virologist. Sequencing of the DENV genome will be performed to monitor DENV variants. Viral genome sequence analysis will be performed by sequencing the NS4B gene and other regions of the DENV genome (if warranted) to characterize DENV variants associated with resistance to JNJ-64281802. Additional exploratory virology analyses may be performed with these samples.

Circulating DENV serotypes/genotypes and genetic variants among index cases and HHCs will be assessed by RT-qPCR and DENV whole genome sequencing at the discretion of the sponsor's virologist.

Immune Assessments

Blood samples for detection of DENV infection as measured by increase in anti-DENV antibody levels will be performed. The level of anti-DENV antibodies will be measured using an ELISA-based assay. The presence of nAbs against DENV and other flaviviruses will be determined using an assay such as microneutralization assay.

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.

Safety assessments will include the monitoring of AEs, physical examinations, vital signs measurements, ECGs, and clinical laboratory tests. DENV-associated signs and symptoms (systemic solicited AEs; see table below), AEs, and concomitant medication will be recorded by the participant in a diary. For oral measurement of body temperature at home to assess fever, participants will be provided with a thermometer.

Solicited Adverse Events

Systemic Reactogenicity
- Retro-orbital pain
- Abdominal pain
- Arthralgia
- Fever
- Headache
- Nausea
- Fatigue
- Myalgia
- Loss of appetite
- Vomiting
- Diarrhea
- Rash

PHARMACOKINETIC EVALUATIONS

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, the following PK parameters and exposure information of JNJ-64281802 can be derived using population PK modeling: AUC_{τ} (if data allow), C_{trough}, and C_{max} (if data allow).

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

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

PHARMACOGENOMIC (DNA) EVALUATIONS

Participant participation in pharmacogenomic research is optional.

Optional blood samples for pharmacogenomic (deoxyribonucleic acid [DNA]) research may be collected, preferably before the first dose of study intervention. If necessary, the sample may be collected at a later time point without constituting a protocol deviation. This DNA sample can be used to investigate the potential association of host genetic factors with PK, antiviral activity, safety of JNJ-64281802, the DENV infection or dengue disease, or may be used to develop tests/assays related to JNJ-64281802 or DENV infection.

BIOMARKER EVALUATIONS

Blood samples for exploratory analysis of biomarkers will be obtained. These samples may be assessed for serum proteins, RNA expression profiling, immune cell components, proteomics, metabolomics, or microbiome. Samples can only be used for research related to JNJ-64281802, DENV infection, or dengue disease, or may be used to develop tests/assays related to JNJ-64281802 or DENV infection. Results may be reported separately from the Clinical Study Report.

OTHER VIROLOGY ASSESSMENTS

NS1 Test and RT-PCR of Index Cases

An acute DENV infection of the index case will be assessed by the detection of the NS1 protein using a diagnostic NS1 test, DENV RNA using DENV RT-PCR, or anti-DENV IgM using an anti-DENV IgM test.

PHARMACOKINETIC SUBSTUDY

In a PK substudy, rich serial PK blood sampling for the measurement of plasma concentrations of JNJ-64281802 will be performed. This substudy will be conducted at selected study sites in 30-40 participants who will be evenly distributed (1:1:1 ratio) over HDR, LDR, and placebo regimen (see Overall Design section). Participants included in the PK substudy will also undergo all assessments in the main study.

At selected study sites participating in the PK substudy, the ICF will contain a separate section explaining the substudy and separate consent will be given for this substudy.

Participants in the substudy will undergo rich serial PK sampling as indicated in Section 1.3.2.5, Pharmacokinetic Substudy.

STATISTICAL METHODS

The study has an event-driven design where study recruitment will continue until the required number of events is reached. The study consists of 2 stages with an IA at the end of Stage 1 and a FA at the end of Stage 2 (ie, the end of the study). The objective of Stage 1 is to obtain proof-of-concept (PoC) for the primary hypothesis. The objectives of Stage 2 are to select the dose for future development and to confirm superiority of the selected dose above placebo.

The IA will be scheduled when 24 laboratory-confirmed DENV infections are observed between baseline and the last day of dosing for the primary hypothesis in the primary analysis population. Based on the results from the IA and other available information from other studies (eg, human challenge), the LDR can be dropped in Stage 2.

The IA will be performed by an independent statistical support group and will be reviewed by the IDMC who will receive unblinded safety and efficacy data. After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study. Refer to the Interim Analysis section for more information on the planned IA.

Unless stopped for futility at the IA, the study will continue till 36 DENV infections are observed between baseline and the last day of dosing in the primary study population and 24 symptomatic DENV infections are observed between baseline and the last day of dosing in the complete study population. Both conditions need to be satisfied before recruitment is considered complete.

Sample Size Calculation

The targets of 36 DENV infection events between baseline and the last day of dosing in the primary study population and 24 symptomatic DENV infections between baseline and the last day of dosing in the complete study population were selected to ensure at least 80% power for the primary and key secondary analyses for the HDR assuming a 75% prophylactic efficacy against DENV infection in the primary study population (using a 2.5% one-sided significance level) and 72.5% prophylactic efficacy against symptomatic DENV infection in the complete study population (using a 20% one-sided significance level). These targets and resulting sample size were estimated through Monte Carlo simulation. More details of the sample size calculations, including sample size simulation programs, will be provided in the Statistical Analysis Plan and a separate Modeling and Simulation report.

As a consequence of the event-driven design of the study, the study has no fixed sample size.

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[redacted]

Populations for Analysis Sets

Population	Description
Enrolled	All participants (index cases and HHCs) who signed the ICF.
Index Case population	All participants enrolled as an index case, with a laboratory-confirmed DENV infection.
Randomized	All participants (HHCs) who are randomized in the study.
Safety	All randomized participants who received at least one dose of study intervention. This population will be used for the safety analysis.
Primary study population	All randomized participants who received at least one dose of study intervention and who had no evidence of current DENV infection (based on negative results for DENV RNA and NS1 protein assays) at baseline. This population will be used for the primary, secondary, and exploratory efficacy analyses.
Secondary study population	All randomized participants who received at least one dose of study intervention, who had evidence of current DENV infection (based on positive results for DENV RNA or NS1 protein assays) but without DENV signs and symptoms at baseline. This population will be used to evaluate the exploratory objective of an antiviral effect of JNJ-64281802 as early treatment.
Complete study population	All randomized participants who received at least one dose of study intervention and without DENV signs and symptoms at baseline. This population will be used to investigate the key secondary endpoint of the effect of JNJ-64281802 on the prevention of symptomatic DENV infection.
PK	All participants who received at least one dose of study intervention and who have at least one plasma concentration value after dosing. This population will be used to the assess the PK and the relationship between PK and the antiviral activity of JNJ-64281802.

DENV = dengue virus; HHC = household contact; ICF = informed consent/assent form; PCR = polymerase chain reaction; PK = pharmacokinetic(s).

Primary Endpoint

The primary endpoint is defined as presence or absence of a laboratory-confirmed DENV infection between baseline and the last day of dosing. Laboratory-confirmed DENV infection is defined as a positive DENV RNA or DENV NS1 protein test result. Missing results between baseline and last day of dosing will not be considered for the primary endpoint.

The primary estimand attributes are as follows.

Population: Healthy HHCs, aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to 65 years inclusive, who have negative results for DENV RNA and NS1 protein assay at baseline. HHCs for which only one of both assays is available will be included on condition that this assay has a negative result.

Interventions: Participants will receive a high- or low-dose JNJ-64281802 regimen, or matching placebo in a double-dummy fashion under fed conditions (see Description of Interventions section).

Intercurrent Events:

- Fasted intake of study intervention.
- Prohibited medication.
- Missed doses and treatment discontinuation: Missing a LD, 2 consecutive MDs, or 2 nonconsecutive MDs within a week.

These intercurrent events will be handled using a "treatment policy strategy" (ie, data will be used as observed).

Population-level Summary: Calculated prophylactic efficacy (= 1 - odds ratio ≈ 1-relative risk rate).

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to prevention of laboratory-confirmed DENV infection between baseline and the last day of dosing.

The primary hypothesis will be evaluated based on the comparison between intervention groups using confidence intervals (CIs), estimates, and p-values obtained from an exact logistic regression model with intervention group and the stratification factor (country) as independent variables. The odds-ratio from the logistic regression model will be used to estimate prophylactic efficacy. Given the expected low incidence, this is thought to be similar to the prophylactic efficacy estimated using relative risk. The calculated prophylactic efficacy (= 1 - odds ratio ≈ 1 - relative risk rate) will be used as the population-level summary. For the PoC stage (Stage 1), the superiority of JNJ-64281802 above placebo will be tested at 20% one-sided significance level. In the confirmatory stage (Stage 2) a 2.5% one-sided significance level will be used. The individual 2-sided CIs (2 x one-sided significance level) for the prophylactic efficacy will be calculated from the regression model described above. This is the primary efficacy analysis. As a secondary estimator, the Mantel-Haenszel stratum-weighted estimator of the risk difference, adjusted for the stratification factor (country) will be calculated together with the associated CIs.

At the IA, the HDR and LDR will be tested hierarchically: First HDR will be tested and if PoC is reached for HDR, the LDR will be tested. Based on these results and other available information (refer to Interim Analysis section), the LDR can be dropped in Stage 2.

At the FA, the primary objective will be assessed using the following hierarchical hypothesis testing approach:

1. In the first step, the HDR will be compared with placebo.
2. If the LDR is not dropped at the IA and a significant reduction in laboratory-confirmed DENV infections is established for the HDR, the LDR will be compared with placebo with regards to the primary endpoint.

Key Secondary Endpoint

The key secondary endpoint is defined as presence or absence of laboratory-confirmed symptomatic DENV infection between baseline and last day of dosing. Laboratory-confirmed symptomatic DENV infection is defined as having at least 2 solicited systemic AEs (see Safety Evaluations section), of which at least one is a most common dengue symptom (ie, fever, headache/retro-orbital pain, myalgia, arthralgia, rash), lasting for ≥1 day and occurring within a +/-2-day window around the positive PCR or NS1 test, between baseline and the last day of dosing.

The key secondary objective will only be assessed at the FA if a significant reduction in the number of laboratory-confirmed DENV infections in the primary study population is established for the HDR. The key secondary objective will be assessed by estimating the prophylactic efficacy of the intervention group(s) in preventing laboratory-confirmed symptomatic DENV infection in the complete study population together with the 80% one-sided lower confidence limit for this prophylactic efficacy. Depending on the result of the primary analysis for the LDR, the key secondary objective will be assessed by:

1. Comparing the pooled number of events on HDR and LDR with the placebo regimen, if both active intervention groups showed a significant effect in the primary study analysis population.
2. Comparing the number of events of the HDR with the placebo regimen, if only the HDR showed a significant effect in the primary study analysis population.

Laboratory-confirmed symptomatic DENV infections will be analyzed similarly as the primary endpoint with the model adjusted for DENV infection at baseline as well.

Secondary Endpoints

All secondary endpoints will be analyzed graphically and descriptively as described in the Statistical Analysis Plan (SAP). For continuous variables, descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum, and 95% CIs) will be calculated. For categorical variables, frequency tables and corresponding 95% CIs will be presented.

Safety Analyses

Adverse Events

For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. Solicited AEs will be summarized by intervention group. All AEs will be analyzed descriptively.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, who experience a severe or a serious AE, or who experience rashes requiring rash-management procedures (Section 10.2).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Frequency tabulations of the laboratory abnormalities will be made either by grading according to the modified Division of Acquired

Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, supplemented with WHO toxicity grading scales t, or with classes for below, within, and above normal ranges for parameters that are not graded for either DAIDS and WHO grading scales. 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 (Grade 3 or Grade 4) will also be provided.

Electrocardiograms

The effects on cardiovascular variables will be evaluated by means of descriptive statistics. These tables will include observed values and changes from baseline values (the last observed ECG prior to the first study intervention administration will be used as baseline).

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT corrected for heart rate (QTc) interval using the following correction methods: QTc according to Bazett's formula (QTcB) and QTc according to Fridericia's formula (QTcF).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

Vital Signs

Vital signs including pulse/heart rate and systolic and diastolic blood pressure (supine) 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.

Pharmacokinetic Analyses

The JNJ-64281802 plasma PK samples taken from all participants in the study (see Sections 1.3.2.2 to 1.3.2.4), as well as the rich serial PK samples collected in the PK substudy (Section 1.3.2.5) can be used for population PK model development and/or population PK model update using nonlinear mixed-effects modeling. Population PK modeling can be used to describe the concentration-time profiles and estimate the exposure parameters (AUC_{τ}, C_{trough}, and C_{max}, if data allow) of JNJ-64281802. Available baseline participant characteristics may be explored as potential covariates affecting PK parameters of JNJ-64281802.

For the intensive PK samples of the rich PK substudy, noncompartmental PK analysis of JNJ-64281802 will be performed using actual sampling time and plasma concentrations obtained from rich serial PK blood sampling for 30-40 participants. Descriptive statistics will be provided for the PK parameters (C_{trough}, C_{max}, time to maximum concentration [t_{max}], C_{min}, and AUC_{τ}) derived, including graphical analyses of the data.

Pharmacokinetic/Pharmacodynamic Analyses

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

Exploratory Endpoints

The statistical analysis of the exploratory endpoints will be described in the SAP.

Interim Analysis

After the review of the IA results, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study (see below for details). An IDMC charter will be prepared before start of the study with more details on the IDMC and Sponsor Committee composition and organization.

The aim of the IA at the end of Stage 1 is to assess PoC of the HDR and LDR for the primary objective. In this analysis, PoC is defined as a statistically significant reduction in the number of laboratory-confirmed DENV infections on active prophylactic dosing compared with placebo at the 20% one-sided significance level. The HDR and LDR will be tested hierarchically: First HDR will be tested and if PoC is reached for the HDR, the LDR will be tested. Based on these results, the IDMC can advise to:

- Stop the study for futility, or
- Drop the LDR and continue the study with placebo regimen and the HDR, or
- Continue the study with both active intervention groups (HDR and LDR) and placebo.

If the study continues, the IDMC may advise to open study recruitment to adolescent HHCs via protocol amendment.

The IDMC advice will be based on the following decision rule:

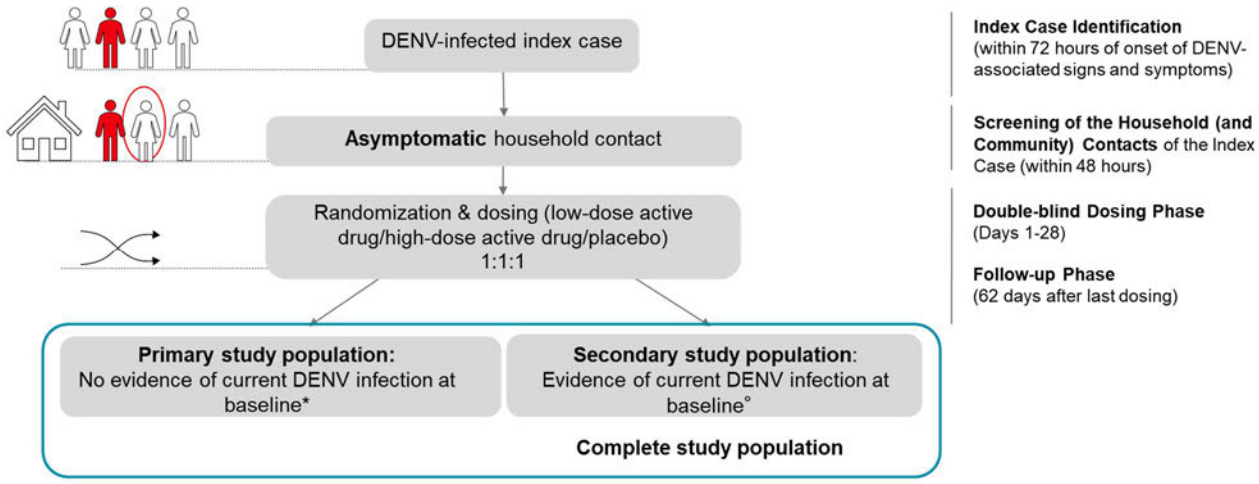
- If PoC is not reached for the HDR, the IDMC can advise to stop the study.
- If PoC is reached for the HDR but not for the LDR, the IDMC can advise to continue the study with only the HDR and placebo regimen and drop the LDR from the study.
- If PoC is reached for both HDR and LDR, the IDMC can advise to continue the study with both active intervention groups and placebo.

However, this rule is non-binding and based on a full review of all safety, efficacy, and exposure-response data available for the current study. In addition, data from other studies (eg, human challenge) may be available to guide the decision.

As the study design only allows for futility assessment at the IA, no multiplicity correction will be performed for the IA. In addition, the impact of potentially dropping the LDR at the IA on the comparison of the HDR with the placebo regimen at the FA was assessed through analytical derivation of the Type I error rate. This analysis showed the Type I error was well controlled (Type I error rate <2.5%).

1.2. Schema

Figure 1: Schematic Overview of the Study



* Based on negative results for DENV RNA and NS1 protein assays
° Based on positive results for DENV RNA or NS1 protein assays
For the definition of index case and HHC, refer to the Overall Design section in the Synopsis.

1.3. Schedule of Activities

1.3.1. Index Cases

Visit Day	Day 1	
Study Procedure		**Notes**
Screening / Administrative		
ICF	X	Must be signed before any study-related activity. Informed consent may be obtained remotely.
Inclusion/exclusion criteria	X	
Blood sample collection to confirm dengue infection: DENV NS1 test[a] in local laboratory	X	Test results of a NS1 test[a] that were performed outside the study by local standard-of-care ≤72 hours of screening may be used for screening of this study.
Antiviral Activity Assessments		
Blood sample collection for DENV VL determination: RT-qPCR in central laboratory	X	
Viral Genome Sequencing		
Blood sample collection for viral genome sequencing	X	
Ongoing Participant Review		
AEs[b]	X	

DENV = dengue virus; ICF = informed consent/assent form; NS = nonstructural protein; RT-(q)PCR = (quantitative) reverse transcription polymerase chain reaction; VL = viral load.

a. If DENV NS1 test is not available, RT-PCR or anti-DENV IgM test in a local laboratory can be used.

b. Only AEs that are related to blood sample procedures will be captured from signing ICF until Day 7. Index cases should actively contact the site if AEs related to the blood sample procedure should occur between the visit day and Day 7.

1.3.2. Household Contacts

1.3.2.1. Screening Phase

Visit Day	-12 hours[a]	
Study Procedure		**Notes**
Study Visit / Contact		
On-site visit	X	
Screening / Administrative		
ICF	X	Must be signed before any study-related activity. Informed consent may be obtained remotely. At selected study sites participating in the PK substudy, the ICF will contain a separate section explaining the substudy and separate consent will be given for this substudy.
Demographics	X	
Medical history and concomitant diseases	X	
Inclusion/exclusion criteria	X	
BMI	X	
Height	X	
Body weight	X	
Urine pregnancy test	X	For all women.
Safety Assessments		
12-lead ECG	X	Should be performed after ≥5 minutes rest in supine position. ECGs are recommended to be performed before vital signs.
Vital signs	X	Systolic and diastolic blood pressure and pulse/heart rate (supine after ≥5 minutes rest). Vital signs are recommended to be assessed after 12-lead ECG.
Physical examination	X	The physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological.
Body temperature	X	Body temperature is to be measured orally in the absence of antipyretic medication, or at least 4 hours after the last intake of antipyretic medication (if applicable).
Ongoing Participant Review[b]		
Concomitant therapy	X	
AEs	X	

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; HHC = household contact; ICF = informed consent form.

Notes:

Refer to Section 1.3.2.4 for assessments to be performed in case of discontinuation of study intervention or the study.

a. Screening for eligible HHC(s) will be performed within 48 hours of obtaining informed consent of the index case. HHCs should start study intervention intake within 12 hours of signing their ICF.

b. Throughout the study from signing of the ICF (AEs) and from the screening visit (concomitant therapy) 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.

1.3.2.2. Double-blind Prophylactic Dosing of HHCs: Day 1 to Day 13

Phase	Double-blind Prophylactic Dosing													
Visit Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Visit Window					**± 1d**				**± 1d**				**± 1d**	
Study Procedure														**Notes**
Study Visit / Contact														
On-site visit or visit at home[a,b]	X	X	X		X				X				X	
Distribution of wallet (study) card	X													
Distribution of paper diary and thermometer	X													Oral body temperature, DENV-associated signs and symptoms (systemic solicited AEs, including fever by oral measurement of body temperature), AEs, and concomitant medication, whether a meal was taken prior to administration of study intervention, and date/time of study intervention intake will be recorded by the participant in a diary, except for the assessments specified in Section 1.3.2.4, Discontinuation From Study Intervention or Study, that will be collected by study site personnel.
Study Intervention Administration														
Randomization	❶													HDR, LDR, or placebo regimen.
Administer study intervention[b]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	X	LD twice daily for 48 hours, followed by a MD once daily for 26 days, under fed conditions (for details, refer to the Description of Interventions section). Whether a meal was taken prior to administration of study intervention, and date/time of study intervention intake will be recorded by the participant in a diary. Administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site.
Dispense study intervention[f]	X	X												
Accountability of study intervention		X	X		X				X				X	
Antiviral Activity Assessments														
Blood sample collection for DENV VL determination (RT-qPCR, NS1 testing)	❶				X				X				X	

Phase	Double-blind Prophylactic Dosing													
Visit Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Visit Window					**± 1d**				**± 1d**				**± 1d**	
Study Procedure														**Notes**
Immune Assessments														
Blood sample collection for humoral immunity (IgG and IgM)	❶				X				X				X	
Blood sample collection for humoral immunity (nAb)	❶													
Viral Genome Sequencing														
Blood sample collection for viral genome sequencing	❶				X				X				X	Viral sequencing will only be performed on DENV RNA positive samples.
Safety Assessments														
Suspected DENV-associated signs and symptoms (systemic solicited AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	DENV-associated signs and symptoms will be recorded daily in a diary by the participant. In case a particular systemic solicited AE was not observed at time of recording but occurs later that day, the participant should record this. In case the systemic solicited AE is fever, oral body temperature should also be recorded.
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	Body temperature is to be measured orally in the absence of antipyretic medication, or at least 4 hours after the last intake of antipyretic medication (if applicable). Will be recorded daily in a diary by the participant (preferably at the same time each day) and in case of feeling feverish. Will be added to the CRF by study site personnel in case the oral body temperature is ≥37.5°C (99.5°F).
Clinical Laboratory Tests														
Blood sample collection for hematology	❶[g]												X	
Blood sample collection for serum chemistry	❶[e, g]												X	
Blood sample collection for coagulation	❶[e, g]												X	
Urine sample collection for urinalysis	❶												X	Urinalysis including dipstick, microscopic sediment examination, and quantitative protein determination.
Pharmacokinetics														
Blood sample collection for PK	❶		X		X				X				X	Blood collections for PK assessments should be kept as close to the specified time as possible. For participants in the PK Substudy, see also Section 1.3.2.5,

Phase	Double-blind Prophylactic Dosing													
Visit Day	1	2	3	4	5	6	7	8	9	10	11	12	13	
Visit Window					± 1d				± 1d				± 1d	
Study Procedure														**Notes**
														Pharmacokinetic Substudy.
Pharmacogenomics (DNA)														
Blood sample collection for host genetics analyses	❶													An optional DNA sample for research (where local regulations permit) may be collected after providing consent in a separate ICF. The sample should preferably be collected before the first dose of study intervention; however, if necessary, it may be collected at a later time point without constituting a protocol deviation.
Biomarkers														
Blood sample collection for host RNA assessments	❶				X									
Blood sample collection for exploratory biomarker research	❶				X									
Ongoing Participant Review[d]														
Concomitant therapy	- - - - - - - - - - - - Continuous - - - - - - - - - - - -													Will be recorded in a diary by the participant.
AEs	- - - - - - - - - - - - Continuous - - - - - - - - - - - -													Will be recorded in a diary by the participant.

❶ = predose.

AE = adverse event; CRF = case report form; DENV = dengue virus; DNA = deoxyribonucleic acid; HDR = high-dose JNJ-64281802 regimen; HHC = household contact; ICF = informed consent form; Ig = immunoglobulin; LD = loading dose; LDR = low-dose JNJ-64281802 regimen; MD = maintenance dose; nAb = neutralizing antibody; NS = nonstructural protein; PK = pharmacokinetic(s); RT-qPCR = quantitative reverse transcription polymerase chain reaction; RNA = ribonucleic acid; VL = viral load.

Notes:

Refer to Section 1.3.2.4 for assessments to be performed in case of discontinuation of study intervention or the study.

a. Visiting the site is required on Days 1, 2, and 28. All other visits may either be performed at the site or by designated study site personnel who visits the participant at home. A time window of +/- 1 day for both site and home visits is allowed as indicated, to ensure at least 2 visits per week at least 2 days apart and maximally 4 days in between blood samples.
b. HHCs should start study intervention intake within 12 hours of signing their ICF. Between on-site visits as indicated in this Schedule of Activities, administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site. MDs will start after the last LD and need to be taken once daily, approximately around the same timepoint every day, until Day 28.
c. On Day 1, the first administration of study intervention will take place at the site. The second administration of study intervention will take place at home. Administration of the third dose of study intervention will be at the site and the fourth dose will be taken at home. LDs need to be taken twice daily, approximately around the same timepoints.
d. Throughout the study from signing of the ICF (AEs) and from the screening visit (concomitant therapy) 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.

e. Two samples will be obtained: one sample to be analyzed by the local laboratory and the other sample to be analyzed by the central laboratory.
f. For Days 1 and 2, blisters will be provided with LD and MD, respectively.
g. If a participant reports with 2 or more ≥ Grade 2 laboratory abnormalities at baseline (Day 1) for ALT, AST, creatinine, lipase, absolute neutrophil count, platelet count, or hemoglobin, the investigator should assess whether the study intervention discontinuation criteria are met (Refer to section 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL), since laboratory results will not be available at randomization. Discontinuation of study intervention should only occur after a confirmatory retesting result.

1.3.2.3. Double-blind Prophylactic Dosing of HHCs (Day 14 to Day 28) and Follow-up Phase

Phase	Double-blind Prophylactic Dosing															Follow-up				
Visit Day	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28 EOD**	**40[a]**	**50[a]**	**60, 70, 80**	**90[a]**	
Visit Window				**± 1d**				**± 1d**				**± 1d**			**± 1d**	**± 2d**	**± 2d**	**±2d**	**± 2d**	
Study Procedure																				**Notes**
Study Visit / Contact																				
On-site visit or visit at home[b]				X				X				X			X	X	X		X	
Phone call visit																		X		
Return of paper diary and thermometer															X					
Study Intervention Administration																				
Administer study intervention[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					MD once daily under fed conditions (for details, refer to the Description of Interventions section). Whether a meal was taken prior to administration of study intervention and date/time of study intervention intake will be recorded by the participant in a diary. Administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site.
Return of study intervention															X					On Day 28, all study intervention dispensed to the participant should be returned to the site.
Accountability of study intervention				X				X				X			X					
Antiviral Activity Assessments																				
Blood sample collection for DENV VL determination (RT-qPCR, NS1 testing)[d]				X				X				X			X	X	X		X	If a participant shows signs and symptoms of DENV infection between Day 28 and Day 90, they must contact the study site and additional blood will be drawn at the study site or their home for antiviral activity assessment and viral genome sequencing,
Immune Assessments																				
Blood sample collection for humoral immunity (IgG and IgM)[d]				X				X				X			X	X	X		X	
Blood sample collection for																X	X		X	

Phase	Double-blind Prophylactic Dosing														Follow-up				
Visit Day	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28 EOD**	**40[a]**	**50[a]**	**60, 70, 80**	**90[a]**	
Visit Window				**± 1d**				**± 1d**				**± 1d**			**± 1d**	**± 2d**	**± 2d**	**±2d**	**± 2d**	
Study Procedure																				**Notes**
humoral immunity (nAb)[d]																				
Viral Genome Sequencing																				
Blood sample collection for viral genome sequencing[d]				X				X				X			X	X	X		X	Viral sequencing will only be performed on DENV RNA positive samples.
Safety Assessments																				
Physical examination																	X			The physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological.
Suspected DENV-associated signs and symptoms (systemic solicited AEs) [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Will be recorded daily in a diary by the participant until Day 28. In case a particular systemic solicited AE was not observed at time of recording but occurs later that day, the participant should record this. In case the systemic solicited AE is fever, body temperature should also be recorded.
Vital signs[d]															X		X			Systolic and diastolic blood pressure and pulse/heart rate (supine after ≥5 minutes rest).
Body temperature[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Oral body temperature is to be measured in the absence of antipyretic medication, or at least 4 hours after the last intake of antipyretic medication (if applicable) until Day 28. Will be recorded daily in a diary by the participant (preferably at the same time each day) and in case of feeling feverish. Will be added to the CRF by study site personnel in case the body temperature is ≥37.5°C (99.5°F).
12-lead ECG[d]															X					Should be performed after ≥5 minutes rest in supine position. See also Section 1.3.2.5, Pharmacokinetic Substudy.
Urine pregnancy test															X		X			For all women.

Phase	Double-blind Prophylactic Dosing														Follow-up				
Visit Day	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 EOD	40[a]	50[a]	60, 70, 80	90[a]	
Visit Window				± 1d				± 1d				± 1d			± 1d	± 2d	± 2d	±2d	± 2d	
Study Procedure																				**Notes**
Clinical Laboratory Tests																				
Blood sample collection for hematology[d]															X		X			
Blood sample collection for serum chemistry[d]															X		X			
Blood sample collection for coagulation[d]															X		X			
Urine sample collection for urinalysis															X					Urinalysis including dipstick, microscopic sediment examination, and quantitative protein determination.
Pharmacokinetics																				
Blood sample collection for PK[d]								X							X	X	X		X	Applicable to all participants. For participants in the PK Substudy, see also Section 1.3.2.5, Pharmacokinetic Substudy.
Biomarkers																				
Blood sample collection for host RNA assessments[d]															X	X				
Blood sample collection for exploratory biomarker research[d]															X	X				
Ongoing Participant Review[e]																				
Concomitant therapy	- - - - - - - - - - - - - - - - Continuous - - - - - - - - - - - - - - - -																			Will be recorded in a diary by the participant until Day 28.
AEs	- - - - - - - - - - - - - - - - Continuous - - - - - - - - - - - - - - - -																			Will be recorded in a diary by the participant until Day 28[f]

❶ = predose.

AE = adverse event; CRF = case report form; DENV = dengue virus; ECG = electrocardiogram; EOD = end of dosing; HHC = household contact; ICF = informed consent form; Ig = immunoglobulin; nAb = neutralizing antibody; NS = nonstructural protein; PK = pharmacokinetic(s); RT-qPCR = quantitative reverse transcription polymerase chain reaction; RNA = ribonucleic acid; VL = viral load.

Note:

Refer to Section 1.3.2.4 for assessments to be performed in case of discontinuation of study intervention or the study.

a. If participants show signs or symptoms of DENV infection between Day 28 and Day 90, they must contact the study site. Additional blood for anti-viral activity assessment and viral sequencing will be drawn at the study site or at their home. Safety will be monitored through AE reporting.
b. Visiting the site is required on Days 1, 2, and 28. All other visits may either be performed at the site or by designated study site personnel who visits the participant at home. A time window of +/- 1 day from Day 1 to Day 28 and +/- 2 days after Day 28 for both site and home visits is allowed as indicated, to ensure at least 2 visits per week at least 2 days apart and maximally 4 days in between blood samples.
c. Between on-site visits as indicated in this Schedule of Activities, administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site. MDs need to be taken approximately at the same timepoint every day.
d. If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: 12-lead ECGs, vital signs, blood draw. Compared to Day 1, where parallel testing is mandatory, parallel (central and local lab analysis) testing is allowed at other timepoints at the discretion of the local PI and Sponsor.
e. Throughout the study from signing of the ICF (for both AEs and concomitant therapy) 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.
f. After Day 28, the participant should contact the site in case any solicited AE, fever, or suspected DENV-associated signs and symptoms (systemic AEs) are experienced, and an additional follow-up visit should be scheduled.

1.3.2.4. Discontinuation From Study Intervention or Study

Visit Day	Withdrawal Visit[a]	Follow-up Visit[a]	
Visit Window			
Study Procedure			**Notes**
Study Visit / Contact			
On-site visit or visit at home[b]	X	X	
Return of diary and thermometer	X		
Study Intervention Administration			
Return of study intervention	X		At the withdrawal visit, all study intervention dispensed to the participant should be returned to the site.
Accountability of study intervention	X		
Antiviral Activity Assessments			
Blood sample collection for DENV VL determination (RT-qPCR, NS1 testing)[c]	X	X	
Immune Assessments			
Blood sample collection for humoral immunity (IgG and IgM)[c]	X	X	
Blood sample collection for humoral immunity (nAb)[c]	X	X	
Viral Genome Sequencing			
Blood sample collection for viral genome sequencing	X	X	Viral sequencing will only be performed on DENV RNA positive samples.
Safety Assessments[d]			
Physical examination	X	X	The physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological.
Vital signs[c]	X	X	Systolic and diastolic blood pressure and pulse/heart rate (supine after ≥5 minutes rest).
Body temperature	X	X	Body temperature is to be measured orally in the absence of antipyretic medication, or at least 4 hours after the last intake of antipyretic medication (if applicable) and will be assessed by study site personnel.
12-lead ECG[c]	X	X	Should be performed after ≥5 minutes rest in supine position.
Urine pregnancy test[f]	X		For all women.
Clinical Laboratory Tests[d]			
Blood sample collection for hematology[c]	X	X	
Blood sample collection for serum chemistry[c]	X	X	

Visit Day	Withdrawal Visit[a]	Follow-up Visit[a]	
Visit Window			
Study Procedure			**Notes**
Blood sample collection for coagulation[c]	X	X	
Pharmacokinetics			
Blood sample collection for PK[c]	X	X	
Biomarkers			
Blood sample collection for host RNA assessments[c]	X	X	
Blood sample collection for exploratory biomarker research[c]	X	X	
Ongoing Participant Review[e]			
Concomitant therapy	X	X	Will be collected by study site personnel.
AEs	X	X	Will be collected by study site personnel.

AE = adverse event; DENV = dengue virus; ECG = electrocardiogram; HHC = household contact; ICF = informed consent form; Ig = immunoglobulin; nAb = neutralizing antibody; NS = nonstructural protein; PK = pharmacokinetic(s); RT-qPCR = quantitative reverse transcription polymerase chain reaction; RNA = ribonucleic acid; VL = viral load.

a. Withdrawal from study intervention (including participants meeting the stopping criteria) or study
   If a participant discontinues study intervention prematurely for any reason other than withdrawal of consent before the end of the double-blind prophylactic dosing phase, a withdrawal visit should be scheduled as soon as possible after the decision for discontinuation, followed by a follow-up visit, which is preferably scheduled 13 to 17 days after the last dose study intervention intake, if the condition of participant allows.
   Withdraw of consent
   Participants who withdraw consent from the study will be offered a follow-up visit.
b. The withdrawal visit will be performed at the site. The follow-up visit can occur at the participant's home by designated study site personnel.
c. If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: 12-lead ECGs, vital signs, blood draw. Parallel (central and local lab analysis) testing is allowed at the discretion of the local PI and Sponsor.
d. Safety assessments and safety lab tests at the follow-up visit will be performed at the discretion of the investigator. If safety assessments are not required, follow-up visits can occur remotely.
e. Throughout the study from signing of the ICF (for both AEs and concomitant therapy) 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.
f. In addition to the urine pregnancy test on the withdrawal visit, an additional serum or urine pregnancy test may also be performed during the follow-up visit, 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.

1.3.2.5. Pharmacokinetic Substudy

Participants included in the PK substudy will also undergo all assessments in the main study (refer to Section 1.3.2.2 through Section 1.3.2.4).

Visit Day	1 [f]								2 [f]	3 [f]	28 EOD								29	32
	predose	+1h	+2h	+4h	+6h	+8h	+10h	+12h	+24h	+48h	predose	+1h	+2h	+4h	+6h	+8h	+10h	+12h	+24h	+96h
Study Procedure[a]																				
Study Visit / Contact																				
On-site visit or visit at home[b]	---------- Continuous ----------								X	X	---------- Continuous ----------								X	X
Safety Assessments																				
12-lead ECG[c]										X										
Pharmacokinetics																				
Blood sample collection for PK[d]	❶[e]	X	X	X	X	X	X	❶	X	X[e]	❶[e]	X	X	X	X	X	X	X	X	X

❶ = predose.
ECG = electrocardiogram; EOD = end of dosing; LD = loading dose; PK = pharmacokinetic(s).

Notes:
Refer to Section 1.3.2.4 for assessments to be performed in case of discontinuation of study intervention or the study.

a. If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: 12-lead ECGs, blood draw.
b. Participants will remain at the site during the first 12 hours on Days 1 and 28. Visiting the site is required on Day 2 and Day 3. All other visits (Day 29 and Day 32) may either be performed at the site or by designated study site personnel who visits the participant at home
c. Should be performed after ≥5 minutes rest in supine position.
d. Blood collections for PK assessments should be kept as close to the specified time as possible.
e. For an intensive PK sample scheduled at the same time as a sparse PK sample, the sparse PK sample does not need to be collected.
f. Timing is in relation to the first morning dose (LD) on Day 1.

2. INTRODUCTION

Dengue is caused by any of the 4 antigenically distinct dengue virus (DENV) serotypes (DENV-1, -2, -3, and -4), which belong to the genus *Flavivirus* in the family of the *Flaviviridae*. The DENVs are human pathogens which are 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* (Carrington 2014). Dengue is endemic in more than 125 countries, and it has also again become endemic in the United States of America (USA) and its territories of American Samoa, Puerto Rico, and the US Virgin Islands (CDC 2019a). 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 (WHO 2019a,b).

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 manifest clinically (with any severity of the disease) (Bhatt 2013). On average, each year about 500,000 dengue cases require hospitalization due to severe and life-threatening diseases and up to 25,000 patients die due to dengue.

During a DENV infection, 1 in 4 infections are symptomatic and 1 in 20 cases develop severe dengue (CDC 2019b) 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 infection usually occurs within 4 to 7 days due to a robust innate and adaptive immune response (Whitehorn 2011). However, less than 1% of DENV infections result in severe dengue outcomes such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

People with asymptomatic/pre-symptomatic dengue infection play a key role in dengue transmission dynamics leading to outbreaks and epidemics. Mosquitoes can become infected from people who are viremic with DENV. This can be someone who has a symptomatic dengue infection, someone who is yet to have a symptomatic infection (they are pre-symptomatic), but also people who show no signs of illness as well (they are asymptomatic) (Duong 2015). People with asymptomatic infections are approximately 80% as infectious to mosquitoes as symptomatic people and, at a population level, approximately 88% of infections result from people who display no apparent symptoms at the time of transmission (asymptomatic/pre-symptomatic) (Ten Bosch 2018). These asymptomatic individuals continue to perform their daily activities and thereby play a major role in dengue transmission dynamics. Factors such as population movement, DENV transmission from infected (but asymptomatic) humans to resident mosquitoes and from infected mosquitoes to susceptible humans eventually lead to dengue outbreaks and dengue epidemic expansion at both a local/regional and international level (Grunnill 2018).

Patients with symptomatic dengue have a limited role in dengue transmission dynamics. A study in Iquitos (Peru) compared 2 groups of febrile individuals (dengue-positive and dengue-negative) with an afebrile control group. Compared to participants with no fever, febrile participants spent more time at home and visited fewer locations and were therefore less likely to transmit the virus

(Perkins 2016). It has been estimated that only 1% of DENV transmission is attributable to people with symptomatic infections (Ten Bosch 2018).

The risk of developing DHF/DSS is especially increased after secondary DENV infection with a different serotype than that of the primary infection, due to a process called antibody-dependent enhancement. The non-neutralizing, cross-reactive antibodies generated during the primary infection partially interact with the virus of a different serotype. Consequently, these partially antibody-coated viruses have a higher likelihood to be taken up by crystallizable fragment (Fc)-receptor-bearing cells (Guzman 2010). Overall, this leads to a higher number of infected target cells, a higher viral load (VL), and a higher probability to develop DHF/DSS. Therefore, it is critical to develop an antiviral small molecule which has equipotent efficacy against all 4 serotypes of DENV.

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 from the Philippine market because of safety concerns, which led to revocation of the vaccine's licensure in the Philippines in February 2019. In December 2018, the vaccine was approved in the European Union for the prevention of dengue disease caused by all DENV serotypes (DENV-1, -2, -3, and -4) in individuals 9 to 45 years of age who have been infected with DENV before and who live in areas where this infection is endemic. 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 World Health Organization (WHO) working group for immunization, as a number of factors need further consideration (WHO 2019a, FDA dengvaxia website). 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.

Study 64281802DNG2004 (further referred to as DNG2004) is a Phase 2, randomized, double-blind, placebo-controlled, double-dummy, multicenter trial assessing the efficacy and safety of 2 dose regimens of JNJ-64281802 for the prevention of dengue infection. JNJ-64281802 is a novel, potent, pan-serotypic small-molecule inhibitor of DENV targeting DENV nonstructural protein (NS)4B.

For the most comprehensive nonclinical and clinical information regarding JNJ-64281802, refer to the latest version of the Investigator's Brochure (IB) for JNJ-64281802 (IB JNJ-64281802 2022).

The term "study intervention" throughout the protocol, refers to JNJ-64281802 or placebo.

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". "Participant" refers to household contacts (HHCs), unless index cases are explicitly mentioned. When "participant" is referred to in relation to the informed consent form (ICF), this can be either a HHC or an index case; when "participant" is referred to in relation to the informed assent form, this refers to an index case.

2.1. Study Rationale

Currently, there is no effective prevention or treatment against dengue infection. Due to limitations on the current dengue approved vaccine, the development of drugs for prophylactic use is getting renewed interest as potential alternatives to prevent dengue (Whitehorn 2014). Prophylaxis could be beneficial for travelers to dengue-endemic regions (eg, aid workers, tourists, business and military travelers, and expatriates), as well as for vulnerable populations living in dengue-endemic regions. By preventing viremia and/or reducing VL, DENV infection-associated morbidity and mortality could be reduced remarkably or even prevented (Bhatt 2013).

JNJ-64281802 is a novel anti-DENV small molecule targeting DENV NS4B. It has shown potent antiviral activity against all 4 DENV serotypes in nonclinical studies (IB JNJ-64281802 2022). By disrupting the DENV viral replication, JNJ-64281802 could potentially reduce the VL and/or prevent viremia from emerging and thereby reduce or even prevent DENV infection-associated morbidity and mortality.

Phase 1 first-in-human (FIH) study 64281802DNG1001, further referred to as DNG1001, has been completed. The 2 dose regimens the study is bringing forward, high and low dose, are based on the results from the Phase 1 FIH study DNG1001 and the available in vitro antiviral activity data of JNJ-64281802.

Study DNG2004 is a randomized, double-blind, placebo-controlled Phase 2 study with an index case-based event-driven design that will evaluate the prophylactic efficacy and safety of JNJ-64281802 for the prevention of dengue in dengue-endemic areas. The study is conducted in asymptomatic HHC at baseline. The study consists of 2 stages. The objective of Stage 1 is to obtain proof-of-concept (PoC) for the primary hypothesis. The objectives of Stage 2 for the primary hypothesis are to select the dose for future development and to confirm superiority of the selected dose above placebo.

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 EC_{50} of 0.05 nM with a selectivity index of 48,000 against DENV-2/16681/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 quantitative reverse transcription polymerase chain reaction (RT-qPCR) against a panel of DENV strains belonging to the 4 major serotypes, including laboratory-adapted strains and clinical isolates obtained from several sources. JNJ-64281802 exhibited potent antiviral activity against all 4 DENV serotypes (laboratory-adapted strains and clinical isolates) with sub-nanomolar or low nanomolar median EC_{50} values against most strains, and a high specificity toward DENV.

In Vivo Pharmacology

In DENV-2 inoculated mice treated with JNJ-64281802, dose-dependent viral ribonucleic acid (RNA) reductions in serum CCI [redacted] compared with vehicle treated mice were observed and were associated with a significant effect on survival. In a non-human primate model, no viral RNA was detected at the highest doses of JNJ-64281802 CCI [redacted] against DENV-2/16681 and at 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

CCI [redacted]

Toxicology

In rats, the no observed adverse effect level (NOAEL) after 31 days was 1,000 mg/kg/day (area under the plasma concentration-time curve from 0 to 24 hours [$AUC_{0\text{-}24h}$] = 524,000 and 706,000 ng.h/mL in male and female rats, respectively). Minor reduction in food consumption and minor, non-adverse 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 ($AUC_{0\text{-}24h}$ = 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.

Pharmacokinetics and Metabolism

- CCI [redacted]
- Absorption: JNJ-64281802 was generally slowly absorbed, with moderate oral bioavailability across species (absolute bioavailability: 25% - 66%). In male dogs withheld from food, the highest JNJ-64281802 exposure values (C_{max} and area under the plasma concentration-time curve from 0 hours to infinity [$AUC_{0-\infty}$]) were obtained with a semi-solid hard gelatin capsule (Gelure 44/14); 1.2-fold increase compared with a 100% polyethylene glycol 400 (PEG400) solution. 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: CCI [redacted] via uridine diphosphate-glucuronosyltransferase (UGT)1A9 and possibly UGT1A4, UGT1A8, and UGT1A10. There was no indication of 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 (PK) 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 toward CYP1A2 and CYP2D6 (50% inhibitory concentration [IC_{50}] >30 µM), and inhibition of CYP2C9 (IC_{50} = 3.7 µM), CYP2C8 (IC_{50} = 7.4 µM), and CYP2C19 (IC_{50} = 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.

Clinical Studies

Study 64281802DNG1001

The Phase 1, double-blind, randomized, placebo-controlled, FIH study 64281802DNG1001 (EudraCT number: 2018-002201-62) examined the safety, tolerability, and PK of increasing single (in 39 participants) and multiple oral doses (in 47 participants) of JNJ-64281802 in healthy adult participants. An open-label, randomized, crossover, relative oral bioavailability part (in 36 participants) was included to study the PK and safety following 2 CCI [redacted] formulation concepts compared with an oral solution, 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 was based on time-matched QT interval corrected for heart rate (QTc). Holter data supports the absence of an effect of JNJ-64281802 on cardiac repolarization at the JNJ-64281802 concentration range investigated in Study DNG1001.

Human Pharmacokinetics

Following single-dose administration with JNJ-64281802 (50-1,200 mg), formulated as oral solution, 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 elimination half-life ($t_{1/2}$) 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%.

CCI [redacted]

64281802DNG1006

CCI

64281802DNG1005

In study 64281802DNG1005, CCI

64281802DNG1004

CCI

CCI

2.3. 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 (IB JNJ-64281802 2022).

2.3.1. Risks for Study Participation

All therapies have the potential to cause adverse experiences. To date, clinical data with JNJ-64281802 are available from the Phase 1 FIH study DNG1001, study DNG1004, study DNG1005, and study DNG1006, in healthy adult participants. 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, 400 mg once daily for 31 days, or 800 mg twice daily for 2 days.

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Risks Due to Study Intervention		
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.	Refer to Inclusion Criteria 6, 7, 8 and Exclusion Criterion 14 for women, and Inclusion Criteria 9 and 10 and Exclusion Criterion 15 for men in this study.
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. A causal relationship between the events of rash and the study intervention cannot be excluded.	Additional safety follow-up procedures will apply, as described in the rash management protocol in Appendix 2: Rash Management.
Concomitant vaccination	Concomitant vaccination might have an influence on the safety profile of JNJ-64281802. Likewise, JNJ-64281802 might have an influence on both safety profile and immunogenicity of any concomitant vaccination.	Licensed live attenuated vaccines, except for COVID-19 vaccines and boosters, are disallowed from 28 days before first dose of study intervention until 90 days after last dose of study intervention. Other licensed (not live) vaccines are disallowed, from 7 days before first dose of study intervention until 90 days after last dose of study intervention (refer to Exclusion Criterion 12 and Appendix 4: COVID-19 Appendix).
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 Due to Study Procedures		
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.	All assessments will be performed by qualified study site personnel.

COVID-19 = Coronavirus Disease 2019.

2.3.2. Benefits for Study Participation

Participants taking part in this study might have the benefit of prevention of dengue infection during the course of JNJ-64281802 administration. Results from the proposed study may be useful in developing a new prophylactic compound for dengue.

2.3.3. Benefit-risk Assessment for Study Participation

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 risk of dengue infection.

3. OBJECTIVES AND ENDPOINTS

The design of this study is detailed in Section 4.1. This study will include index cases ≥1 years of age who will participate for one visit only, and HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years who are eligible be included in the intervention part of the study (see Section 5.1, Inclusion Criteria). HHCs must not have DENV-associated clinical signs and symptoms at baseline (see Section 5.2, Exclusion Criteria).

Objectives	Endpoints
Primary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of laboratory-confirmed DENV infection up to the last day of dosing among HHC who have no evidence of current DENV infection at baseline.	• Laboratory-confirmed DENV infection[a] between baseline and the last day of dosing.
Key Secondary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection through development of signs and symptoms up to the last day of dosing (see Table 3) among all HHC.	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing.
Secondary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection through development of signs and symptoms up to the last day of dosing (see Table 3) among HHC who have no evidence of current DENV infection at baseline.	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing.
• To assess the safety and tolerability of 2 dose regimens (high and low) of JNJ-64281802 among HHC.	• Safety and tolerability as measured by recording of adverse events (AEs), serious adverse events (SAEs), physical

Objectives	Endpoints
	examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory assessments.
• To assess the PK of JNJ-64281802 following repeated oral dosing among HHC.	• PK parameters for JNJ-64281802 (area under the concentration curve during one dosing interval [AUC_τ], observed analyte concentration just prior to the beginning or at the end of a dosing interval [C_{trough}], and C_{max}).
• To assess the relationship between the PK and pharmacodynamics (PD), selected antiviral activity of JNJ-64281802, clinical outcome and safety parameters) after repeated dosing of JNJ-64281802 among HHC.	• Laboratory-confirmed DENV infection[a] between baseline and the last day of dosing. • PK (plasma concentrations or exposure parameters) of JNJ-64281802. • Safety parameters. • Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing.
Exploratory	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection up to the last day of dosing as measured by DENV RNA among HHC who have no evidence of current DENV infection at baseline.	• Presence or absence of a positive DENV RNA test result between baseline and the last day of dosing.
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the reduction of DENV RNA among enrolled HHC who have no evidence of current DENV infection at baseline and who are infected post baseline.	• Maximum DENV RNA levels between baseline and last day of dosing.
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection up to the last day of dosing as measured by detection of DENV NS1 protein among HHC who have no evidence of current DENV infection at baseline.	• Presence or absence of a positive DENV NS1 protein test result between baseline and the last day of dosing.
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection as measured by increase in anti-DENV antibodies among HHC who have no evidence of current DENV infection at baseline.	• Increase in anti-DENV antibody between baseline and Day 40 • Increase in anti-DENV antibody between baseline and Day 50 • Increase in anti-DENV antibody between baseline and Day 90

Objectives	Endpoints
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection up to Day 40, 50, and 90 among all HHC who completed study intervention (28 days).	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and Day 40. • Laboratory-confirmed symptomatic DENV infection[b] between baseline and Day 50. • Laboratory-confirmed symptomatic DENV infection[b] between baseline and Day 90.
• To evaluate the antiviral effect of JNJ-64281802 as early treatment among HHC who have evidence of DENV infection at baseline.	• Time to end of detectable DENV RNA and/or reduction in DENV RNA load. • Time to end of detectable DENV NS1 protein. • DENV-associated signs and symptoms.
• To identify circulating DENV serotypes/genotypes and genetic variants among index cases and HHC.	• Serotype/genotype of DENV based on viral genome sequence analysis. • Genetic variation of viral genome sequence based on changes at the amino acid level • Emergent JNJ-64281802 resistance-associated mutations in HHC using index case sequence as reference.

AE = adverse event; DENV = dengue virus; ECG = electrocardiogram; HHC = household contact; nAb = neutralizing antibody; NS = non-structural protein; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetic(s); RNA = ribonucleic acid; SAE = serious adverse event.

[a] Laboratory-confirmed DENV infection is defined as a positive DENV RNA or DENV NS1 protein test result.
[b] Laboratory-confirmed symptomatic DENV infection is defined as having at least 2 solicited systemic AEs (see Table 3), of which at least one is a most common dengue symptom (ie, fever, headache/retro-orbital pain, myalgia, arthralgia, rash), lasting for ≥1 day and occurring within a +/-2 day-window around the positive PCR or NS1 test, between baseline and the last day of dosing.

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

HYPOTHESIS

See Section 9.1, Statistical Hypotheses.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled, double-dummy, multicenter, interventional study, assessing the efficacy and safety of 2 dose regimens of JNJ-64281802 for the prevention of dengue infection in HHCs of a DENV-infected index case.

The study will be conducted in approximately 10 countries in South-East Asia and the American continent.

There are 4 sequential phases in the study: DENV-infected index case identification, screening of the HHCs which may include family members, acquaintances, co-workers, and community

contacts of the index case, double-blind prophylactic dosing of HHCs, and the follow-up phase. Stopping criteria are listed in Section 7.1.1.

The study consists of 2 stages with an interim analysis (IA) planned at the end of Stage 1 and the final analysis (FA) planned at the end of Stage 2 (ie, at the end of the study). The IA will be performed by an independent statistical support group and will be reviewed by the Independent Data Monitoring Committee (IDMC) who will receive unblinded safety and efficacy data (see Section 10.6.6, Committees Structure). After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study (see Section 9.5, Interim Analysis). A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making considering the IDMC recommendation. The FA will be performed by the sponsor who will be fully unblinded to the treatment allocation at that time.

This study consists of a main study (see below) and a PK substudy (see Section 8.9, Pharmacokinetic Substudy).

Assessments and visits to the site will be performed as indicated in the Schedule of Activities. Please refer to Appendix 4: COVID-19 Appendix for guidance on study conduct during the Coronavirus Disease 2019 (COVID-19) pandemic.

DENV-infected Index Case Identification

An index case is a patient (≥1 years old) with laboratory-confirmed dengue identified in the community (ie, hospital and/or health care center [HCC]/health care provider [HCP]). Laboratory-confirmed dengue for an index case is defined as:

1. Any DENV-associated signs and symptoms ≤72 hours of onset (according to Appendix 3: WHO Clinical Classification of Dengue Disease), AND
2. A positive DENV NS1 test at screening. Results from tests performed as part of the local standard-of-care ≤72 hours of screening may be used for screening for this study. If a DENV NS1 test is not available, a DENV PCR test or anti-DENV immunoglobulin M (IgM) test can also be used.

After informed consent/assent is obtained, either at the site or remotely (eg, at the index case's home), a blood sample for viral assessments will be collected, and the person's HHCs will be contacted. If the index case is a minor according to the local laws and regulations, assent and informed consent from the parent(s) or legal guardian(s) or legally acceptable representative(s) will be obtained.

Screening of the Household/Community Contacts of the Index Case

A HHC is a person who lives, spends the night, or regularly attends/shares/consumes cooking/meals in the same dwelling or housing complex as the index case. A household can include one or more families, or community contacts in a single or in multiple houses or dwellings, depending on the country, site, social-economic, and cultural characteristics. Co-workers and

acquaintances can also be considered HHCs, if they spend time together with the index case (eg, early morning hours or twilight hours) can also be considered as HHCs.

HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years can be included in the intervention part of the study. HHC must be asymptomatic at screening and can include participants with no evidence of current DENV infection (consisting of naïve and historical DENV-infected participants) or with evidence of current DENV infection as confirmed by laboratory assessments, performed at a central laboratory on samples taken at baseline (see Section 1.2, Schema).

Screening for eligible HHC(s) will be performed within 48 hours of obtaining informed consent/assent of the index case. For this purpose, HHCs will be invited to the study site. Informed consent of the HHC will be obtained on site or remotely (see Section 10.6.3, Informed Consent Process and Assent Form).

Double-blind Prophylactic Dosing of HHCs

The study is event driven, with a target number of 36 DENV infections observed in the primary study population and a target number of 24 symptomatic DENV infections observed in the complete study population (see Section 9.3, Populations for Analysis Sets). Both conditions need to be satisfied before recruitment is considered complete. Under the current assumptions, between 1,250 and 1,850 participants are expected to be enrolled in the study (see Section 9.2, Sample Size Determination).

Participants will be randomized in a 1:1:1 ratio to receive a high- or low-dose study intervention, or matching placebo in a double-dummy fashion (see Table 2 for details) for 28 days. The study will use randomization at the individual participant level, stratified by country.

- High-dose JNJ-64281802 regimen (HDR):
  - 400 mg JNJ-64281802 loading dose (LD) twice daily for 48 hours, followed by
  - 150 mg JNJ-64281802 maintenance dose (MD) once daily for 26 days.
- Low-dose JNJ-64281802 regimen (LDR):
  - 150 mg JNJ-64281802 (LD) twice daily for 48 hours, followed by
  - 50 mg JNJ-64281802 (MD) once daily for 26 days.
- Placebo (double-dummy; see Table 2).

LDs need to be taken twice daily, approximately around the same timepoints. MDs will start after the last LD and need to be taken once daily, approximately around the same timepoint, until Day 28.

The study intervention is to be taken in fed conditions (for details, see Table 2). Study intervention can be taken with water.

All participants will complete 2 days of LD and 26 days of MD. This is to cover the estimated 3 to 4 weeks *A. Aegypti* lifespan with 10 to 18 days infective life and DENV transmission risk, depending on environmental temperature (Goindin 2015).

Development of DENV-associated clinical signs and symptoms (according to Appendix 3: WHO Clinical Classification of Dengue Disease) will be evaluated and recorded, virologic and serologic testing, and safety assessments will be performed.

In a PK substudy, rich serial PK blood sampling for the measurement of plasma concentrations of JNJ-64281802 will be performed. This substudy will be conducted at selected study sites in 30-40 participants who will be evenly distributed (1:1:1 ratio) over HDR, LDR, and placebo regimen (see Section 8.9, Pharmacokinetic Substudy). Participants included in the PK substudy will also undergo all assessments in the main study.

The study intervention will be dispensed directly to the participants at the site (see Section 6.2, Preparation/Handling/Storage/Accountability).

Follow-up Phase

Double-blind prophylactic dosing of HHCs will be followed by intensive follow-up until Day 50 and a last visit on Day 90. At the end-of-study visit, assessments will be performed as indicated in Section 1.3.2.3. Total study duration will be approximately 13 weeks for HHCs.

4.2. Scientific Rationale for Study Design

Population

Asymptomatic HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years can be included in the intervention part of the study. People in dengue-endemic areas older than 65 years would have already been infected with all 4 dengue serotypes at any time in their lives. As there can be up to 4 DENV serotypes circulating at any time in dengue-endemic regions, the conduct of the study in dengue-naïve as well as dengue-past exposed study participants in endemic regions allows for the assessment of the efficacy of the 2 dose regimens and of the ultimate decision on one dose selection.

Blinding, Control, 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. Administration of study intervention will be in a double-dummy fashion to maintain the blind between the HDR and LDR.

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 (deoxyribonucleic acid [DNA]) 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 is to collect DNA to allow the identification of host genetic factors that may influence the PK, antiviral activity, safety of JNJ-64281802, the DENV infection or dengue disease, or may be used to develop tests/assays related to JNJ-64281802 or DENV infection. An optional blood sample for pharmacogenomic research may be collected (where local regulations permit), preferably at baseline (ie, before first dose of study intervention). Participation in the pharmacogenomic research is voluntary and requires a separate consent.

Biomarker samples will be collected to evaluate the mechanism of action of JNJ-64281802, to help analyze interindividual variability in clinical outcomes, or help to potentially 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 intervention-clinical response relationship. Samples can only be used for research related to JNJ-64281802 or DENV infection, or they 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. Analyses of the DNA and biomarker samples are at the discretion of the sponsor and results may be reported separately.

4.2.1. Study-specific Ethical Design Considerations

This study will also include index cases ≥1 years of age. When "participant" is referred to in relation to the ICF, this can be either a HHC or an index case; when "participant" is referred to in relation to the informed assent form, this refers to an index case.

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/assent 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/assent voluntarily will be enrolled. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

The primary ethical concern is that this study will be performed in asymptomatic HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years without clinical signs and symptoms of dengue. Participants taking part in the study might have the benefit of dengue infection prevention during JNJ-64281802 administration. They will receive financial compensation to a comparable fair market value for the time and inconveniences that may arise from participation in the study per local regulations. Refer to Section 2.3 for details on benefits and risks, and for the safety measures taken to minimize risk to participants.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to approve 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. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) 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/assent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

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 (American Red Cross 2021).

4.3. Justification for Dose

The dosing regimen selection was based on final data from the Phase 1 FIH study DNG1001, interim data from the Phase 1 study DNG1006, final data from the Phase 1 human challenge characterization studies with DENV-1 (CSR DENV-1-LVHC 2021; Endy 2021), Good Laboratory Practice toxicity studies, final data from the non-human primate challenge studies, and in vitro antiviral activity data of JNJ-64281802.

A population PK model was developed using pooled data from DNG1001 (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) and DNG1006 Panels 1-5 (single doses of 50 to 800 mg). CCI [redacted]

CCI [redacted]

The 2 days twice daily administered LDs will be followed by 26 days once daily administered MDs. CCI [redacted] CCI [redacted] The following LD/MD regimens were selected:

- High-dose JNJ-64281802 regimen:
  - 400 mg JNJ-64281802 (LD) twice daily for 48 hours, followed by
  - 150 mg JNJ-64281802 (MD) once daily for 26 days.
- Low-dose JNJ-64281802 regimen:
  - 150 mg JNJ-64281802 (LD) twice daily for 48 hours, followed by
  - 50 mg JNJ-64281802 (MD) once daily for 26 days.

CCI [redacted]

The 28-day dosing period will cover the estimated 3 to 4 weeks *A. Aegypti* lifespan with 10 to 18 days infective life and DENV transmission risk, depending on environmental temperature (Goindin 2015).

Based on population PK simulations, a mean C_{max} and mean AUC_{0-24h} at Day 2 (end of LD period) and Day 28 (end of dosing period) were derived for the selected JNJ-64281802 dosing regimens (Table 1). CCI [redacted] CCI [redacted]

Table 1: CCI

CCI

[redacted]

4.4. End of Study Definition

Index Case

Index case participation in the study will involve only one visit.

Household Contact

End of Study Definition

The end of study is considered as the last visit 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 visit 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 the participant has completed assessments at Day 90.

5. STUDY POPULATION

Patients with laboratory-confirmed dengue (index case) will first be identified (see Section 4.1, Overall Design). HHCs (which may include family members, acquaintances, co-workers, and community contacts) of the index case who have no DENV-associated clinical signs and symptoms at baseline will be enrolled in this study. Screening for eligible HHC(s) will be performed within 48 hours of obtaining informed consent/assent of the index case. HHCs should start study intervention intake within 12 hours of signing their ICF. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

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

Index Cases

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

Age

1. ≥1 years of age.

Type of Participant and Disease Characteristic

2. Criterion modified per Amendment 1.

   2.1 Criterion modified per Amendment 3.

   2.2 Must have laboratory-confirmed dengue infection:

   a. Any DENV-associated signs and symptoms ≤72 hours of onset (according to Appendix 3: WHO Clinical Classification of Dengue Disease), AND

   b. A positive DENV NS1 test at screening. Test results performed by local standard-of-care ≤72 hours of screening may be used for screening for this study. If a DENV NS1 test is not available, a DENV PCR test or anti-DENV IgM test could also be used.

Informed Consent/Assent

3. Must sign an ICF (or their legally acceptable representative must sign) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

   In case the index case has not reached the legal adult age per the local regulation, the signature of a legal representative of the index case will be required. Parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign an ICF indicating that they understand the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study as described in Section 10.6.3, Informed Consent Process and Assent Form.

Household Contacts

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

Age

1. 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age, inclusive.

Type of Participant and Disease Characteristic

2. Healthy on the basis of physical examination, medical history, and vital signs performed at screening. If there are abnormalities, the participant may be included only if the investigator judges the abnormalities to be not clinically relevant. This determination must be recorded in the participant's source documents.

3. Criterion modified per Amendment 3.

   3.1 Must have a blood pressure (participant must be supine for ≥5 minutes):

   For a participant between 16 and 18 years old: between 90 and 120 mmHg systolic, extremes included, and ≤80 mmHg diastolic at screening.

   For a participant >18 years old: between 90 and 140 mmHg systolic, extremes included, and ≤90 mmHg diastolic at screening.

   Two repeat measurements are allowed in the absence of any other concerning health screening issues. If the results of blood pressure are outside these ranges, the participant may be included only if the investigator judges the deviations from normal blood pressure to be not clinically significant or to be appropriate and reasonable for the population under study.

Weight

4. Criterion modified per Amendment 1.

   4.1 Must have a body mass index (BMI, weight in kg divided by the square of height in meters) between 18.0 and 35.0 kg/m^2 inclusive, and a body weight of ≥40.0 kg at screening.

Sex and Contraceptive/Barrier Requirements

5. Man or woman.

6. A woman must have a negative highly sensitive urine pregnancy test at screening.

7. Criterion modified per Amendment 3

   7.1 A woman must be (as defined in Appendix 5: Contraceptive and Barrier Guidance)

   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 ≥90 days after the last dose,

the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.

Examples of highly effective methods of contraception are provided in Appendix 5: Contraceptive and Barrier Guidance.

A woman using hormonal contraception must use an additional barrier-based 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 coadministered with JNJ-64281802 and therefore they should not be considered as a highly effective contraceptive method during dosing with JNJ-64281802.

8. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 6 months after the last dose of study intervention.

9. During the study and for ≥90 days after last dose of 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.

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

Informed Consent

11. Must sign an ICF (or their legally acceptable representative must sign) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

12. Must sign a separate ICF (or their legally acceptable representative must sign) if the participant agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

13. Must be willing and able to adhere to the study requirements and lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Having any DENV-associated clinical signs and symptoms (according to Appendix 3: WHO Clinical Classification of Dengue Disease).

2. Criterion modified per Amendment 1.

   2.1 Criterion modified per Amendment 3.

   2.2. History of liver or renal insufficiency, 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 disturbance, if deemed clinically significant by the investigator.

3. Known allergies, hypersensitivity, or intolerance to JNJ-64281802 or its excipients (refer to the IB for JNJ-64281802 [IB JNJ-64281802 2022]).

4. Criterion modified per Amendment 3.

   4.1 Any clinically relevant skin disease (as assessed by the investigator) in the past 3 months such as, but not limited to, dermatitis, eczema, drug rash, psoriasis, food allergy, and urticaria.

5. Having donated or lost >1 unit of blood (500 mL) within 60 days or >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 during the study or within 6 months after last dose of study intervention.

6. Criterion modified per Amendment 3.

   6.1 Reduced immune function due to:

   a. Known or suspected congenital or acquired immunodeficiency; or

   b. Receipt of immunomodulation therapy within the last 6 months (such as anticancer chemotherapy or radiation therapy).

7. History of risk factors for Torsades de Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome).

8. 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.

Prior/Concurrent Clinical Study Experience

9. Criterion modified per Amendment 1.

   9.1 Criterion modified per Amendment 3.

   9.2 Received an investigational intervention (including investigational vaccines other than a COVID-19 vaccine) or used an invasive investigational medical device within 3 months before the planned first dose of study intervention or received an investigational biologic product within 3 months prior to enrollment or 5 half-lives, whichever is longer, before the planned first dose of study intervention, or is currently enrolled in an investigational study.

Prior/Concomitant Therapy

10. Taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study intervention.

11. Criterion modified per Amendment 3.

    11.1 Use of any strong CYP3A4 inhibitors, strong CYP3A4 inducers, substrates for CYP3A4 with a narrow therapeutic index, or sensitive BCRP substrates within 7 days before first dose of study intervention. Refer to Appendix 10 for examples of such disallowed medications.

12. Criterion modified per Amendment 1

    12.1 Criterion modified per Amendment 3.

    12.2 Received or plans to receive any of the following vaccines:

    a. Licensed live attenuated vaccines are disallowed 28 days before first dose of study intervention until 90 days after last dose of study intervention.
    b. Other licensed (not live) vaccines are disallowed from 7 days before first dose of study intervention until 90 days after last dose of study intervention.

    Any prior vaccinations against DENV virus are not allowed until 90 days after last dose of study intervention. Vaccinations against all other flaviviruses are not allowed from 28 days before first dose of study intervention until 90 days after last dose of study intervention.

    Participants will be allowed to receive a COVID-19 vaccine (see Appendix 4: COVID-19 Appendix).

13. Use of any immunosuppressive corticosteroids (excluding topical and nasal) or immunosuppressive drugs within 28 days before first dose of study intervention. An

immunosuppressive dose of corticosteroids is defined as ≥10 mg prednisone equivalent per day for ≥14 days.

Other Exclusions

14. Pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.

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

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. The required source documentation to support meeting the enrollment criteria are noted in Appendix 6: 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 6.8, 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. Must refrain from consumption of grapefruit or grapefruit juice from screening until the last PK sample has been taken.

5.3.2. Caffeine, Alcohol, and Drugs of Abuse

1. Must limit the use of food or drinks/beverages containing alcohol to the absolute minimum from screening until the last PK sample has been taken. If any alcohol is taken, ≤2 standard drink consumptions daily will be allowed. A standard drink is defined as a 350-mL glass of 5% alcohol-by-volume (ABV) beer, a 150-mL glass of 12% ABV wine, or a 45-mL glass of 40% ABV (80 proof) spirit.

2. Must refrain from all use of energy drinks and avoid excessive use of caffeine from screening until the last PK sample has been taken. 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).

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 investigator will not generate screening and enrollment logs directly from the interactive web response system (IWRS).

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/assent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent/assent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants must be assigned new participant numbers.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

HHCs should start study intervention intake within 12 hours of signing their ICF.

Participants will be randomized to study intervention as described in Section 4.1, Overall Design and receive study intervention in a double-dummy fashion under fed conditions as presented in Table 2. Study intervention can be taken with water.

Study intervention will be dispensed at the site or by designated study site personnel who visits the participant at home as indicated in the Schedule of Activities. Study site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol. All intakes of study intervention from Day 1 to Day 28 will take place at the study site or at home.

On Day 1, the first administration of study intervention will take place at the site. The second administration of study intervention will take place at home. Administration of the third dose of study intervention will be at the site and the fourth dose will be taken at home.

Participants in the PK substudy must take the first dose of study intervention on site in the morning to allow for the hourly PK sample collection. The second dose of study intervention should be taken in the evening at the site.

MD starts after LD (on Day 3) and should be taken once daily, at approximately the same time of the day, until Day 28.

CCI [redacted]

Whether a meal was taken prior to administration of study intervention and date/time of study intervention intake must be captured in the diary and the case report form (CRF). See also Section 6.2, Preparation/Handling/Storage/Accountability and Section 6.4, Study Intervention Compliance.

JNJ-64281802 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for JNJ-64281802 for a list of excipients (IB JNJ-64281802 2022).

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

Table 2: Description of Study Intervention

Intervention Name	JNJ-64281802	Placebo
Dose Formulation	CCI	
Unit Dose Strength(s)		
Dosage Level(s) and Frequency	• High-dose regimen: ○ 400 mg JNJ-64281802 (LD) twice daily for 48 hours, followed by ○ 150 mg JNJ-64281802 (MD) once daily for 26 days • Low-dose regimen: ○ 150 mg JNJ-64281802 (LD) twice daily for 48 hours, followed by ○ 50 mg JNJ-64281802 (MD) once daily for 26 days	Placebo will be administered in a double-dummy fashion so that there is only one placebo group with administration of study intervention at the same frequency as the active intervention groups.
Number CCI	CCI	
Route of Administration	Oral	Oral
Food/Fasting Requirement	The study intervention is to be taken in fed conditions, ie, within 30 minutes after the start of the participant's regular meal (eg, breakfast, lunch, snack, and/or dinner).	The study intervention is to be taken in fed conditions, ie, within 30 minutes after the start of the participant's regular meal (eg, breakfast, lunch, snack, and/or dinner).
Use	Experimental	Placebo
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Table 2: Description of Study Intervention

Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	JNJ-64281802 will be provided in blisters in child resistant packaging.	Placebo will be provided in blisters in child resistant packaging.

IMP = investigational medicinal product; LD = loading dose; MD = maintenance dose.

6.2. Preparation/Handling/Storage/Accountability

Study intervention will be self-administered and/or administered by designated study site personnel when the participant visits the site or is visited at home. For details, see Section 6.4, Study Intervention Compliance.

Preparation/Handling/Storage

The study intervention will be dispensed directly to the participants at the site by designated study site personnel who will adhere to privacy requirements approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).

All study intervention must be stored at controlled temperatures as indicated on the product-specific labeling. On Day 1, participants will be instructed on how to store the study intervention at home.

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 dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants, or their legally acceptable representatives where applicable, must be instructed to return all blisters, whether empty or containing study intervention. The study intervention administered to the participant must be documented on the intervention accountability form. Participants will note study intervention administration in a diary. All study intervention will be stored and disposed of according to the sponsor's instructions.

Study intervention must be handled in strict accordance with the protocol, and the study intervention 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 sponsors study site monitor during on-site monitoring visits. 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.

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. Whenever a participant brings his or her study intervention to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. For administration of study intervention at the site, the investigator agrees to not store the study intervention at any

site other than the study sites agreed upon with the sponsor. The investigator agrees to administer the study intervention only at the study site or at the participants' home. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual/study-site investigational product and procedures manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be assigned to 1 of 3 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. A separate randomization list will be created for the PK substudy.

The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention serum 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.

Under normal circumstances, the blind should not be broken 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 contacting the IWRS. 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 IWRS and in the appropriate section of the CRF. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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, for the IA (see Section 9.5, Interim Analysis), 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 IA. Sponsor personnel involved in the PK and exposure-response modeling will have access to the PK and PD data before formal unblinding. Sponsor personnel involved in study conduct, data management, and statistics will not have access to these data.

6.4. Study Intervention Compliance

Study intervention will be self-administered and/or administered by designated study site personnel when the participant visits the site or is visited at home. Visits to the study site are indicated in the Schedule of Activities:

- For the main study:
  - Visiting the site is required on Days 1, 2, and 28. All other visits as indicated in the Schedule of Activities may either be performed at the site or by designated study site personnel who visits the participant at home. Between on-site visits, administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site. MDs need to be taken approximately at the same timepoint every day.
- For the PK substudy:
  - Participants will remain at the site during the first 12 hours on Days 1 and 28. Visiting the site is required on Day 2 and Day 3. All other visits (Day 29 and Day 32) may either be performed at the site or by designated study site personnel who visits the participant at home.

Study intervention will be administered orally, and date/time of study intervention intake will be recorded by the participant in a diary.

When the participant visits the site, study intervention will be administered by designated study site personnel who will check the participant's mouth to confirm that the dose was swallowed. The date and time of each dose administered in the study site will be recorded in the source documents for on-site administration and recorded in the CRF. The intake 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.

When participants self-administer study intervention at home, compliance with study intervention will be assessed as indicated in the Schedule of Activities. Administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site (also see Section 8, Study Assessments and Procedures).

Participants will receive instructions on compliance with study intervention administration on Day 1. During the study, the investigator or designated study site personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the study intervention.

Compliance will be assessed by counting returned tablets and review of the diary during the site or home visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

The number of study intervention tablets dispensed will be recorded and compared with the number returned. A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study 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.

6.7. Treatment of Overdose

For this study, any dose of JNJ-64281802 greater than the assigned daily dose within a 24-hour time period (Table 2) will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor immediately.
- Evaluate need to discontinue study intervention in consultation with the Medical Monitor.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until JNJ-64281802 can no longer be detected systemically (at least 46 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the source documents and the CRF.

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

6.8. 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 in the CRF throughout the study from the screening visit 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.

In case any comedications are used, the dose and dosing regimen must be recorded in the Concomitant Therapy Section of the CRF. 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 following medications other than the study intervention are allowed during (a part of) the study:

- The investigator may permit the use of paracetamol/acetaminophen from 3 days before first dose of study intervention until the last PK sample has been taken at ≤3 x 500 mg per day, and ≤3 grams per week. In case paracetamol/acetaminophen is 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. In order to minimize the antipyretic effects of paracetamol/acetaminophen on body temperature outcome readings, participants are recommended not to take paracetamol/acetaminophen within 4 hours before the next body temperature measurement, except those with high fever (≥39°C). In this case, the body temperature before taking paracetamol/acetaminophen, the dose taken, and the body temperature one hour after taking paracetamol/acetaminophen should be recorded in the daily dairy. In addition, the Medical Monitor should be informed about this occurrence.
- Stable HRT (ie, same dose and not starting or stopping HRT for 2 weeks before first dose of study intervention until the end of the study) in postmenopausal women is allowed. It should be noted that JNJ-64281802 may affect the effectiveness of HRT agents when coadministered. The use of HRT must be recorded in the Concomitant Therapy Section of the CRF. Applicable procedures and treatment guidance based on package inserts should be respected.

Other co-medication allowed include the following:

- H_1 receptor antagonists (with exception of mizolastine), topical corticosteroids, or antipruritic agents in the recommended dose scheme.
- H_2 receptor antagonists.
- The use of antiemetics in case of severe nausea.

For vaccinations:

- Participants will be allowed to receive an authorized/licensed COVID-19 vaccine throughout this study (see Appendix 4: COVID-19 Appendix), including attenuated COVID-19 vaccines and boosters.
- Other licensed live attenuated vaccines are not allowed from 28 days before first dose of study intervention until 90 days after last dose of study intervention. Furthermore, other licensed (not live) vaccines, are disallowed from 7 days before first dose of study intervention until 90 days after last dose of study intervention.

- Any prior vaccinations against DENV virus are not allowed until 90 days after last dose of study intervention. Vaccinations against all other flaviviruses are not allowed from 28 days before first dose of study intervention until 90 days after last dose of study intervention.

Participants must not use any immunosuppressive corticosteroids (excluding topical and nasal) or immunosuppressive drugs from 28 days before first dose of study intervention until 28 days after last dose of study intervention. 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 must not use any anticoagulant medication or NSAIDs including aspirin, from screening until the last study visit. Aspirin and NSAIDs can interfere with the ability of the blood to clot. It is not anticipated that any participants will have severe DENV infection with bleeding problems, however, it is still recommended to avoid these drugs. The investigator may recommend paracetamol/acetaminophen or an equivalent at doses described above.

Use of any strong CYP3A4 inhibitors, strong CYP3A4 inducers, substrates for CYP3A4 with a narrow therapeutic index, or sensitive BCRP substrates from 7 days before first dose of study drug until 28 days after last dose of study drug is not permitted. 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.

Refer to 10.10 Appendix 10: Examples of Disallowed Medications for examples of such disallowed medications.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Participant Discontinuation Criteria

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, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant.
- As baseline (Day 1) laboratory results will not be available at randomization, any participant who reports with 2 or more ≥ Grade 2 laboratory abnormalities for ALT, AST, creatinine, lipase, absolute neutrophil count, platelet count, or hemoglobin at baseline, must be discontinued. Discontinuation of study intervention should only occur after a confirmatory retesting result and if deemed clinically significant by the investigator.

- Noncompliance with study intervention administration occurs, defined as missing a LD, 2 consecutive MDs, or 2 nonconsecutive MDs within a week (judged case-by-case after discussion between the Sponsor and investigator).
- In case of abnormal liver tests as outlined in 10.11 Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments and Section 7.1.2 Participant Stopping Criteria due to Liver Chemistry .

If a participant discontinues study intervention prematurely for any reason other than withdrawal of consent before the end of the double-blind prophylactic dosing phase, a withdrawal visit should be scheduled as soon as possible after the decision for discontinuation, followed by a follow-up visit, which is preferably scheduled 13 to 17 days after the last dose study intervention intake, if the condition of participant allows (see Section 1.3.2.4, Discontinuation From Study Intervention or Study). Blood sample should be collected at the withdrawal and follow-up visits for immune assessments, viral analysis, viral genome sequencing, and safety assessments (at the follow-up visit, safety assessments should occur at the discretion of the investigator).

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will be entered to ensure the protocol-specified number of participants complete the study.

Please refer to Appendix 4: COVID-19 Appendix for guidance on study conduct during the COVID-19 pandemic.

7.1.1. Participant Stopping Criteria due to DENV infection

In addition to the discontinuation criteria outlined in Section 7.1 above, HHCs who develop DENV-associated clinical warning signs and symptoms (according to Appendix 3: WHO Clinical Classification of Dengue Disease) during the study and require hospitalization will be withdrawn from study intervention. The participant will perform a withdrawal and safety follow-up visit as described in Section 7.1, Discontinuation of Study Intervention.

The participant will receive medical care according to local standards. Hospitalization is classified as SAE and should be reported accordingly (see Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting).

7.1.2. Participant Stopping Criteria due to Liver Chemistry

Stopping of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in 10.11 Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments, after consultation with the sponsor, or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.3. Study Pausing Criteria

If significant safety concerns arise following administration of study intervention (and a specific set of study pausing criteria have been met), further randomization and dosing of participants may be paused.

The reasons for pausing the study are listed below. The list only applies for events that are considered by the investigator to be related to study intervention and unrelated to dengue disease or an associated infection (eg, COVID-19).

- Death of a participant, considered related to study intervention or if the causal relationship to the study intervention cannot be excluded; OR
- Three or more participants at one study site or six or more participants at all study sites experience a ≥Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor) that is considered related to study intervention;

  Note: An AE report based on a ≥Grade 3 laboratory abnormality will only be considered if the laboratory abnormality is clinically significant and persistent (upon repeated testing) per the investigator. Elevations of total cholesterol will not be considered.

  OR
- Any safety findings that in the opinion of the sponsor or the IDMC warrants pausing (or cessation) of dosing.

To enable a prompt response to a situation that could trigger the study pausing criteria, the investigator should notify the sponsor's medical monitor (or designee) immediately and no later than 24 hours after becoming aware of any ≥Grade 3 unsolicited AE considered related to study intervention (and update the CRF with relevant information on the same day the AE information is collected). A thorough analysis of all reported ≥Grade 3 unsolicited AEs will initially be carried out by the sponsor's medical monitor (or designee). Based on the available data, the sponsor's medical monitor (or designee) will determine whether a safety data review by the IDMC is warranted, to assess whether the study pausing criteria are met.

If the IDMC judges that the study pausing criteria have been met, the IDMC will recommend to either pause the study or to implement modifications to the study conduct and/or to the safety assessments. If safety concerns would occur only with the HDR, the IDMC may recommend to pause randomization and dosing in the HDR group but continue randomization and dosing in the LDR and placebo groups.

In case the IDMC recommends a study pause, all sites/investigators will be notified immediately of the pause by the sponsor's medical monitor (or designee).

In case a safety data review by the IDMC was triggered because three or more participants at one study site or six or more participants at all study sites experienced a ≥Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor) that is determined to be related to study intervention, the IDMC will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or to the safety assessments to the Sponsor Committee to ensure the safety of enrolled participants. The IDMC can recommend to the Sponsor Committee to halt a dose arm or to pause or stop the study due to safety concerns.

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
- Failure to comply with the protocol requirements or to cooperate with the study site personnel

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document.

For participants who discontinue the study prematurely for reasons other than withdrawal of consent, a withdrawal visit and a follow-up will be performed (see Section 7.1, Discontinuation of Study Intervention and Section 1.3.2.4, Discontinuation From Study Intervention or Study).

HHCs who withdraw consent from the study will be offered a follow-up visit. Index cases who withdraw consent/assent during screening (ie, their only visit in the study) will not be followed up.

Withdrawal of Consent/Assent

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

A participant who withdraws from the study will have the following options regarding the optional research samples (only applicable to pharmacogenomic research samples; see Section 8.5):

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for the optional research samples, ie, samples for pharmacogenomic analysis, in which case, the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for the optional pharmacogenomic research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research While Remaining in the Main Study

The participant may withdraw consent for use of samples for additional future research (refer Section 10.6.5, Long-term Retention of Samples for Additional Future Research). 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 the optional pharmacogenomics research samples.

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 the participant 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. 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), and to determine the reason for discontinuation/withdrawal. 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 sampling to enable assessment of antiviral activity, viral genome sequencing, PK, immune, biomarker, pharmacogenomic, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: 12-lead ECGs, vital signs, blood draw. Compared to Day 1, where parallel testing is mandatory, parallel (central and local lab analysis) testing is allowed at other time points at the discretion of the local PI and Sponsor. Blood collections for antiviral activity and PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier/later than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation and CRF.

The total blood volume to be collected from each HHC will not exceed 450 mL. For index cases, the total blood volume collected will be approximately 5 mL for those <18 years old and approximately 10 mL for those ≥18 years old.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

A urine drug screen (including amphetamine, barbiturate, benzodiazepine, cannabinoids, cocaine, methadone, opiates, and tricyclic antidepressants) and alcohol test may be performed throughout the study at the discretion of the investigator.

Oral body temperature (daily and in case of feeling feverish), DENV-associated signs and symptoms (systemic solicited AEs, including fever by oral measurement of body temperature), AEs, and concomitant medication, whether a meal was taken prior to administration of study intervention, and date/time of study intervention intake will be recorded by the participant in a diary (except for the assessments specified in Section 1.3.2.4, Discontinuation From Study Intervention or Study, that will be collected by study site personnel) and will be added to the CRF by study site personnel. Body temperature will only be added to the CRF in case the oral body temperature is ≥37.5°C (99.5°F). If the participant is unable to read or write, an acceptable representative of the participant may complete the diary (which includes reading and explaining all written information).

Telehealth Visits

Refer to Section 6.4, Study Intervention Compliance and Schedule of Activities.

Telehealth visits (conducted via phone or video conference) may be implemented by or with approval from the sponsor and per the clinical judgment of the investigator, where feasible and permissible by local policy.

How the assessments performed at each visit are collected (via on-site visit, home health care, or telehealth visit) must be recorded in the CRF.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF, laboratory requisition form, and the source documents.

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 collection, and visits to the study site:

- For the main study:
  - Visiting the site is required on Days 1, 2, and 28. All other visits as indicated in the Schedule of Activities may either be performed at the site or by designated study site personnel who visits the participant at home. A time window of +/- 1 day for both site and home visits is allowed as indicated in the Schedule of Activities, to ensure at least 2 visits per week at least 2 days apart and maximally 4 days in between blood samples. Between on-site visits, administration of study intervention will either be at home (including remote supervision of study intervention intake, if feasible) or participants may come to the site. MDs need to be taken approximately at the same timepoint every day. Follow-up visits on Days 40, 50, and 90 should take place within a window of +/- 2 days.
- For the PK substudy:
  - Participants will remain at the site during the first 12 hours on Days 1 and 28. Visiting the site is required on Day 2 and Day 3. All other visits (Day 29 and Day 32) may either be performed at the site or by designated study site personnel who visits the participant at home.

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 for JNJ-64281802 (IB JNJ64281802 2022)
- Study protocol
- Sample ICF

- Participant (paper) diary
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- Electronic data capture (eDC) manual
- Contact Information page(s)
- Any other manual, as applicable

8.1. Efficacy

8.1.1. Virology

8.1.1.1. Antiviral Activity

Blood sampling for DENV VL determination will be performed at the time points indicated in the Schedule of Activities.

Antiviral activity will be assessed by measuring DENV RNA levels and DENV NS1 protein levels in serum of the HHCs. Serum DENV RNA levels will be assessed using a validated quantitative DENV RT-PCR assay and serum DENV NS1 protein levels will be assessed using an enzyme-linked immunosorbent assay (ELISA)-based assay. For a subset of samples (including but not limited to RNA positive samples), the NS1 serum levels may be analyzed by a diagnostic assay at the discretion of the sponsor's virologist. Details of the assays used will be provided in the laboratory manual.

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

8.1.1.2. Viral Genome Sequencing and Dengue Virus Serotyping

Blood sampling for viral genome sequence analysis on index cases and HHCs will be performed at the time points indicated in the Schedule of Activities. Viral sequencing will only be performed on DENV RNA positive samples at the discretion of the sponsor's virologist.

Sequencing of the DENV genome will be performed to monitor DENV variants. Viral genome sequence analysis will be performed by sequencing the NS4B gene and other regions of the DENV genome (if warranted) to characterize DENV variants associated with resistance to JNJ-64281802. Additional exploratory virology analyses may be performed with these samples.

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

Circulating DENV serotypes/genotypes and genetic variants among index cases and HHCs will be assessed by RT-qPCR and DENV whole genome sequencing at the time points indicated in the Schedule of Activities, at the discretion of the sponsor's virologist.

8.1.2. Immune Assessments

Blood samples for detection of DENV infection as measured by increase in anti-DENV antibody levels will be performed at the time points indicated in the Schedule of Activities. The level of anti-DENV antibodies will be measured using an ELISA-based assay. The presence of nAb against DENV and other flaviviruses may be determined using an assay such as micro-neutralization assay for a subset of samples at the time points indicated in the Schedule of Activities and at the discretion of the sponsor's virologist. Details of the assays used will be provided in the laboratory manual.

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

8.2. Safety Assessments

Details regarding the IDMC are provided in Section 10.6.6, Committees Structure.

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.

Safety assessments will include the monitoring of AEs, physical examinations, vital signs, ECGs, and clinical laboratory tests. In addition, DENV-associated clinical signs and symptoms will be recorded as solicited AEs (see Section 8.3.2, Method of Detecting Adverse Events and Serious Adverse Events).

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 7: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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.

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

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities. Additional safety assessments may be performed at the discretion of the investigator.

8.2.1. Physical Examinations

Physical examination and height and body weight measurements will be conducted.

Physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological.

To obtain the actual body weight, participants must be weighed lightly clothed and barefoot. The height should be measured barefoot. The same weighing scale will preferably be used.

8.2.2. Vital Signs

Oral body temperature (in the absence of antipyretic medication or at least 4 hours after the last intake of antipyretic medication (if applicable)), pulse/heart rate, and systolic and diastolic blood pressure will be assessed. Vital signs are recommended to be assessed before blood draw and after 12-lead ECG.

Blood pressure and pulse/heart rate measurements will be assessed in supine position, if possible with a completely automated device consisting of an inflatable cuff and an oscillatory detection system. 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).

Body temperature will be recorded by the participant in a diary daily (preferably at the same time each day) and in case of feeling feverish, and will be added to the CRF by study site personnel in case the oral body temperature is ≥37.5°C (99.5°F).

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.

For eligibility determination, the machine-read ECG results, printed on the ECG device print-out of the ECG tracing, will be taken into account. These ECGs need to be interpreted for clinical significance, signed, and dated by the investigator and filed in participant's source documents. Clinically relevant abnormalities occurring during the study should be recorded by the investigator in the Adverse Event Section of the CRF.

Central ECG readings will be performed by a central ECG laboratory. Instructions for ECG acquisition and ECG transmission will be described in the manual provided by the ECG laboratory. There will be 2 ECG reports: A preliminary report and a final report.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology and coagulation, and a urine sample for other tests will be collected as noted in Appendix 8: 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.

8.2.5. Pregnancy Testing

All women must have a negative highly sensitive urine pregnancy test at screening and on Days 28 and 50. A pregnancy test will also be performed during the withdrawal visit. Additional serum or urine pregnancy tests may also 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.

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaint (PQC), 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. Adverse events and concomitant medication will be recorded by the participant in a diary, except in case of discontinuation of study intervention or study (see Section 1.3.2.4) where they will be collected by study site personnel.

For further details on AEs, SAEs, and PQC refer to Appendix 7: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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 AEs 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, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

For any ≥Grade 3 unsolicited AE, whether serious or non-serious, the investigator will as soon as possible assess the possible relationship to study intervention. If the investigator considers the ≥Grade 3 unsolicited AE to be related to study intervention, the investigator will notify the sponsor’s medical monitor (or designee) immediately and no later than 24 hours after becoming aware of the AE.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs 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 an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined events for which the participant is specifically questioned. Signs and symptoms of DENV infection (DENV-infection associated AEs) will be collected by the investigator or designee as solicited AEs (Table 3). DENV-associated signs and symptoms (systemic solicited AEs) will be recorded daily by the participant in a diary. In case a particular systemic solicited AE was not observed at time of recording but occurs later that day, the participant should record this. In case the systemic solicited AE is fever, oral body temperature should also be recorded. For oral measurement of body temperature at home to assess fever, participants will be provided with a thermometer.

All AEs are evaluated using the gradings presented in Table 4, the modified DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events supplemented with WHO toxicity grading scales in Section 10.9 , or the rash management protocol in Section 10.2.

Table 3: Solicited Adverse Events

Systemic Reactogenicity
- Retro-orbital pain [a]
- Abdominal pain [a]
- Arthralgia [a]
- Fever [b]
- Headache [b]
- Nausea [b]
- Fatigue [b]
- Myalgia [b]
- Loss of appetite [a]
- Vomiting [b]
- Diarrhea [b]
- Rash [c]

a. Grading according to Table 4.
b. Grading according to the modified DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events supplemented with WHO toxicity grading scales in Section 10.9.
c. Grading according to the rash management protocol in Section 10.2.

Table 4: Grading of Solicited Adverse Events

Reaction to Intervention	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 (eg inadequate oral caloric intake and/or fluid intake); tube feeding or total parenteral nutrition indicated	Life-threatening consequences; urgent intervention indicated

Unsolicited Adverse Events

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

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events and the special reporting situation of pregnancy will be followed by the investigator as specified in Appendix 7: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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 AEs 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 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 SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from study intervention but can continue to participate in the follow-up period.

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, will be required.

8.3.6. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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

8.4. 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 or antiviral activity aspects that address concerns arising during or after the study period. Samples may also be used for the analysis of metabolites of JNJ-64281802 or endogenous markers for enzymes or transporters involved in the metabolism and distribution of JNJ-64281802, at the discretion of the sponsor. Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

See also Section 8.9, Pharmacokinetic Substudy.

8.4.1. Evaluations

Venous blood samples will be collected for measurement of plasma concentrations of JNJ-64281802.

Samples collected for analyses of JNJ-64281802 plasma concentration may additionally be used to evaluate safety or antiviral activity aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biologic samples can be found in the laboratory manual.

8.4.2. Analytical Procedures

Pharmacokinetics

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 assigned to placebo (except for samples taken predose on Day 1) will not be analyzed unless unexpected results should occur. All plasma PK samples from participants receiving JNJ-64281802 will be analyzed for JNJ-64281802 concentrations.

To allow selection of samples, the bioanalytical laboratory will receive randomization lists per study intervention. 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.

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

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 can be derived using population PK modeling:

- AUC_{τ} (if data allow)
- C_{trough}, and
- C_{max} (if data allow).

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5. Pharmacogenomics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit).

Participant participation in pharmacogenomic research is optional.

Optional blood samples for pharmacogenomic (DNA) research may be collected, preferably before the first dose of study intervention. If necessary, the sample may be collected at a later time point without constituting a protocol deviation. This DNA sample can be used to investigate the potential association of host genetic factors with PK, antiviral activity, safety of JNJ-64281802, the DENV infection or dengue disease, or may be used to develop tests/assays related to JNJ-64281802 or DENV infection.

These analyses may be conducted under the supervision of the sponsor and may be reported separately from the main study report.

8.6. Biomarkers

Blood samples for exploratory analysis of biomarkers will be obtained at the time points indicated in the Schedule of Activities. These samples may be assessed for serum proteins, humoral immunity profiling, RNA expression profiling, immune cell components, proteomics, metabolomics, or microbiome. Samples can only be used for research related to JNJ-64281802, DENV infection, or dengue disease, or may be used to develop tests/assays related to JNJ-64281802 or DENV infection. Results may be reported separately from the Clinical Study Report.

8.7. Other Virology Assessments

8.7.1. NS1 Test and RT-PCR/anti-DENV IgM test of Index Cases

An acute DENV infection of the index case will be assessed at the local laboratory or site by the detection of the NS1 protein using a diagnostic NS1 test. If a DENV NS1 test is unavailable, a DENV RT-PCR or anti-DENV IgM test can be used. Detection of DENV RNA will be confirmed by RT-qPCR at the central laboratory. If anti-DENV IgM and IgG antibodies are included in the NS1 test, these data should be captured.

8.8. Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9. Pharmacokinetic Substudy

In a PK substudy, rich serial PK blood sampling for the measurement of plasma concentrations of JNJ-64281802 will be performed. This substudy will be conducted at selected study sites in

30-40 participants who will be evenly distributed (1:1:1 ratio) over HDR, LDR, and placebo regimen (see Section 4.1, Overall Design).

At selected study sites participating in the PK substudy, the ICF will contain a separate section explaining the substudy and separate consent will be given for this substudy.

Participants included in the PK substudy will also undergo all assessments in the main study.

Participants in the substudy will undergo rich serial PK sampling as indicated in Section 1.3.2.5.

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 efficacy and safety data are outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to prevention of laboratory-confirmed DENV infection between baseline and the last day of dosing in study participants who are DENV RNA and NS1 protein negative at baseline. Laboratory-confirmed DENV infection is defined as a positive DENV RNA or DENV NS1 protein (ELISA) test result.

9.2. Sample Size Determination

The study has an event-driven design where study recruitment will continue until the required number of events is reached. Unless stopped for futility at the IA, the study will continue till 36 DENV infections are observed between baseline and the last day of dosing in the primary study population and 24 symptomatic DENV infections are observed between baseline and the last day of dosing in the complete study population (see Section 9.3, Populations for Analysis Sets). Both conditions need to be satisfied before recruitment is considered complete.

The targets of 36 DENV infection events in the primary study population and 24 symptomatic DENV in the complete study population were selected to ensure at least 80% power for the primary and key secondary analyses for the HDR assuming a 75% prophylactic efficacy against DENV infection in the primary study population (using a 2.5% one-sided significance level) and 72.5% prophylactic efficacy against symptomatic DENV infection in the complete study population (using a 20% one-sided significance level). These targets and resulting sample size were estimated through Monte Carlo simulation. More details of the sample size calculations, including sample size simulation programs, will be provided in the SAP and a separate Modeling and Simulation report.

As a consequence of the event-driven design of the study, the study has no fixed sample size.

However, the planned recruitment total is estimated based on the following information:

CCI

[redacted]

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants (index cases and HHCs) who signed the ICF.
Index Case population	All participants enrolled as an index case, with a laboratory-confirmed DENV infection.
Randomized	All participants (HHCs) who are randomized in the study.
Safety	All randomized participants who received at least one dose of study intervention. This population will be used for the safety analysis.
Primary study population	All randomized participants who received at least one dose of study intervention and who had no evidence of current DENV infection (based on negative results for DENV RNA and NS1 protein assays) at baseline. This population will be used for the primary, secondary, and exploratory efficacy analyses.
Secondary study population	All randomized participants who received at least one dose of study intervention, who had evidence of current DENV infection (based on positive results for DENV RNA or NS1 protein assays) but without DENV signs and symptoms at baseline. This population will be used to evaluate the exploratory objective of an antiviral effect of JNJ-64281802 as early treatment.
Complete study population	All randomized participants who received at least one dose of study intervention and without DENV signs and symptoms at baseline. This population will be used to investigate the key secondary endpoint of the effect of JNJ-64281802 on the prevention of symptomatic DENV infection.
PK	All participants who received at least one dose of study intervention and who have at least one plasma concentration data value after dosing.

Population	Description
	This population will be used to the assess the PK and the relationship between PK and the antiviral activity of JNJ-64281802.

DENV = dengue virus; HHC = household contact; ICF = informed consent/assent form; PCR = polymerase chain reaction; PK = pharmacokinetic(s).

9.4. Statistical Analyses

The SAP 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.

9.4.1. General Considerations

The study has an event-driven design where study recruitment will continue until the required number of events is reached. The study consists of 2 stages with an IA after Stage 1 and a FA after Stage 2 (ie, the end of the study). The objective of Stage 1 is to obtain PoC for the primary hypothesis. The objectives of Stage 2 are to select the dose for future development and to confirm superiority of the selected dose above placebo.

The IA will be scheduled when 24 laboratory-confirmed DENV infections are observed between the baseline and the last day of dosing in the primary analysis population. Based on the results from the IA and other available information, the LDR can be dropped in Stage 2.

The IA will be performed by an independent statistical support group and will be reviewed by the IDMC who will receive unblinded safety and efficacy data (see Section 10.6.6, Committees Structure). After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study. Refer to Section 9.5, Interim Analysis for more information on the planned IA.

Unless stopped for futility at the IA, the study will continue till 36 DENV infections are observed between baseline and the last day of dosing in the primary study population and 24 symptomatic DENV infections are observed between baseline and the last day of dosing in the complete study population (see Section 9.2, Sample Size Determination). Both conditions need to be satisfied before recruitment is considered complete.

All demographic characteristics (eg, age, race, ethnicity, height, body weight, BMI) and other initial participant characteristics (eg, medical and surgical history, concomitant diseases) will be tabulated and analyzed descriptively for the index case population (when applicable), the safety population, the primary, secondary, and the complete study populations.

Descriptive statistics will be provided for the disease characteristics of the index case population.

9.4.2. Primary Endpoint(s)

Definition

The primary endpoint is defined as the presence or absence of a laboratory-confirmed DENV infection between baseline and the last day of dosing. Laboratory-confirmed DENV infection is defined as a positive DENV RNA or DENV NS1 protein (ELISA) test result. Missing results between baseline and last day of dosing will not be considered for the primary endpoint.

Estimand

The primary estimand attributes are as follows.

Population

Healthy HHCs, aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to 65 years inclusive, who have negative results for DENV RNA and NS1 protein assay at baseline. HHCs for which only one of both assays is available will be included on condition that this assay has a negative result.

Interventions

Participants will receive a high- or low-dose JNJ-64281802 regimen, or matching placebo in a double-dummy fashion under fed conditions (see Table 2).

Intercurrent Events

- Fasted intake of study intervention.
- Prohibited medication.
- Missed doses and treatment discontinuation: Missing a LD, 2 consecutive MDs, or 2 nonconsecutive MDs within a week.

These intercurrent events will be handled using a "treatment policy strategy" (ie, data will be used as observed).

Population-level Summary

Calculated prophylactic efficacy (=1 - odds ratio ≈ 1-relative risk rate).

Primary Estimator

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to prevention of laboratory-confirmed DENV infection between baseline and last day of dosing.

The primary hypothesis will be evaluated based on the comparison between intervention groups using CIs, estimates, and p-values obtained from an exact logistic regression model with intervention group and the stratification factor (country) included as independent variables. The odds-ratio from the logistic regression model will be used to estimate the prophylactic efficacy. Given the expected low incidence, this is expected to be similar to the prophylactic efficacy estimated using the relative risk. The calculated prophylactic efficacy (= 1 - odds ratio ≈ 1 - relative

risk rate) will be used as the population-level summary. For the PoC stage (Stage 1), the superiority of JNJ-64281802 above placebo will be tested at 20% one-sided significance level. In the confirmatory stage (Stage 2) a 2.5% one-sided significance level will be used. The individual 2-sided CIs (2 x one-sided significance level) for the prophylactic efficacy will be calculated from the regression model described above. This is the primary efficacy analysis. As a secondary estimator, the Mantel-Haenszel stratum-weighted estimator of the risk difference, adjusted for the stratification factor (country) will be calculated together with the associated CIs.

At the IA, the HDR and LDR will be tested hierarchically: First the HDR will be tested and if PoC is reached for the HDR, the LDR will be tested. Based on these results and other available information (refer to Section 9.5, Interim Analysis), the LDR can be dropped in Stage 2.

At the FA, the primary objective will be assessed using the following hierarchical hypothesis testing approach:

1. In the first step, the HDR will be compared with placebo.
2. If the LDR is not dropped at the IA and a significant reduction in laboratory-confirmed DENV infections is established for the HDR, the LDR will be compared with placebo with regards to the primary endpoint.

Sensitivity Estimators

Sensitivity estimators will be calculated as follows:

- Handling the intercurrent events in a 'while on treatment strategy': Only laboratory assessments prior to the occurrence of the intercurrent events are considered.
- Restricting the population to the HHCs who completed treatment up to Day 28.
- Early dropout and intermediate missing values: Fitting an exact Poisson regression with the event rate, defined as the number of cases over the number of samples (offset) as dependent variable and the intervention group and country as independent variables. For cases, the number of samples is defined as the number of samples between start of study intervention and the occurrence of the first event (first laboratory-confirmation of the DENV infection), for non-cases, it is the number of samples between start of study intervention and the last available sample before or at the last day with study intervention. Thus, all participants are included in the analysis according to their number of available samples.

9.4.3. Key Secondary Endpoint

The key secondary endpoint is defined as presence or absence of laboratory-confirmed symptomatic DENV infection between baseline and last day of dosing. Laboratory-confirmed symptomatic DENV infection is defined as having at least 2 solicited systemic AEs (see Table 3), of which at least one is a most common dengue symptom (ie, fever, headache/retro-orbital pain, myalgia, arthralgia, rash), lasting for ≥1 day and occurring within a +/-2-day window around the positive PCR or NS1 test, between baseline and the last day of dosing.

The key secondary objective will only be assessed at the FA if a significant reduction in the number of laboratory-confirmed DENV infections in the primary study population is established for the HDR. The key secondary objective will be assessed by estimating the prophylactic efficacy of the intervention group(s) in preventing laboratory-confirmed symptomatic DENV infection in the complete study population together with the 80% one-sided lower confidence limit for this prophylactic efficacy. Depending on the result of the primary analysis for the LDR, the key secondary objective will be assessed by:

1. Comparing the pooled number of events on the HDR and LDR with the placebo regimen, if both active intervention groups showed a significant effect in the primary study analysis population.
2. Comparing the number of events on the HDR with the placebo regimen, if only the HDR showed a significant effect in the primary study analysis population.

Laboratory-confirmed symptomatic DENV infections will be analyzed similarly as the primary endpoint with the model adjusted for DENV infection at baseline as well.

9.4.4. Secondary Endpoint(s)

All secondary endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, maximum, and 95% CIs) will be calculated. For categorical variables, frequency tables and corresponding 95% CIs will be presented.

9.4.4.1. Safety Analyses

All safety analyses will be made on the safety population. Participants in this population will be defined by the study intervention actually received, not by randomization assignment.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs 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 last day of study participation is considered to be treatment-emergent. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. All AEs will be analyzed descriptively.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, who experience a severe or a serious AE, or who experience rashes requiring rash-management procedures (Section 10.2).

Solicited AEs will be summarized by intervention group. The number and percentages of participants with at least one solicited AE will be presented. The frequencies by intervention group, as well as frequencies according to severity will be described for solicited AEs. Frequencies of unsolicited AEs will be presented by system organ class and preferred term, while those of solicited AEs will be presented only by preferred term.

All AEs are evaluated using the gradings presented in Table 4, the modified DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events supplemented with WHO toxicity grading scales in Section 10.9 , or the rash management protocol in Section 10.2.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Frequency tabulations of the laboratory abnormalities will be made either by grading according to the modified DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events supplemented with WHO toxicity grading scales (Section 10.9), or with classes for below, within, and above normal ranges for parameters that are not graded for either DAIDS and WHO grading scales. 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 (Grade 3 or Grade 4) will also be provided.

Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc interval using the following correction methods: QTc according to Bazett's formula (QTcB) and QTcF (Bazett 1920, Fridericia 1920, Hodges 1983, ICH guidelines 2005).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds. The last observed ECG prior to the first study intervention administration will be used as baseline.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

For the safety substudy, ECGs will be analyzed similarly to ECG statistical analysis as described above.

Vital Signs

Vital signs including pulse/heart rate and systolic and diastolic blood pressure (supine) 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.

9.4.4.2. Pharmacokinetic Analyses

The JNJ-64281802 plasma PK samples taken from all participants in the study (see Section 1.3.2.2 to Section 1.3.2.4), as well as the rich serial PK samples collected in the PK substudy (Section 1.3.2.5) can be used for population PK model development and/or population PK model

update using nonlinear mixed-effects modeling. The PK samples taken from participants in the rich serial PK substudy will also be analyzed by noncompartmental PK analysis as specified below. Population PK modeling can be used to describe the concentration-time profiles and estimate the exposure parameters (AUC_{τ}, C_{trough}, and C_{max}, if data allow) of JNJ-64281802. Available baseline participant characteristics (demographics, body weight, laboratory variables, genotype, etc) may be explored as potential covariates affecting PK parameters of JNJ-64281802. 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 population PK report. For operational reasons, a snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-64281802 and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

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 an SAE.

Pharmacokinetic Substudy Analyses

For the intensive PK samples of the rich PK substudy, noncompartmental PK analysis of JNJ-64281802 will be performed using actual sampling time and plasma concentrations obtained from rich serial PK blood sampling for 30-40 participants. Descriptive statistics will be provided for the PK parameters (C_{trough}, C_{max}, t_{max}, C_{min}, and AUC_{τ}) derived, including graphical analyses of the data. Results will be presented in a separate PK report.

9.4.4.3. Pharmacokinetic/Pharmacodynamic Analyses

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

9.4.5. Exploratory Endpoint(s)

The statistical analysis of the exploratory endpoints will be described in the SAP.

9.4.6. Other Analyses

An IDMC will be established as noted in Section 10.6.6, Committees Structure.

Viral Genome Sequence Analyses

DENV viral genome sequence analysis will be performed to evaluate the presence of polymorphisms and genetic variations on the amino acid level and to define the serotype/genotype of the DENV virus.

Sequencing is focused on a predefined list of positions of interest. Data will be described in the CSR or in a separate virology report.

Samples for viral sequencing are taken throughout the study as shown in the Schedule of Activities, but sequencing is triggered at the discretion of the virologist considering the DENV VL levels and the limitations of the sequencing assay.

Polymorphisms, ie, genetic variations, are defined as amino acid changes from serotype-specific DENV reference sequences.

Wild type: If at certain position the amino acid in the participant sequence matches the reference sequence, that is no genetic variation is present at that position, the virus is considered to be wild type at that position.

Number (%) of participants with a specific substitution and number (%) of participants with a specific DENV serotype/genotype will be analyzed.

Frequencies and percentages will be presented for the specified parameters. The denominator is the number of participants with sequencing data. Summaries will be provided by subgroup and intervention group.

Pharmacogenomic Analyses

The statistical approach for analyzing 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 and will always be under the supervision of the sponsor. Results will be presented in the main study report or a separate report.

DNA samples may be used for pharmacogenomic analyses. Host genetic analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data, and for research related to JNJ-64281802 and comedications, if applicable, or dengue infection or dengue disease. They may also be used to develop tests/assays related to JNJ-64281802 and comedications in the protocol, if applicable, and dengue infection. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to JNJ-64281802 and comedications, if applicable, or dengue clinical endpoints.

Results will be presented in the main study report or a separate report.

Biomarker 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 and will always be under the supervision of the sponsor. Results will be presented in the main study report or a separate report.

9.5. Interim Analysis

The SAP will describe the planned IA in greater detail.

The IA will be performed at a predetermined analysis time point. This time point is defined when 24 laboratory -confirmed DENV infections (see Section 9.4.1, General Considerations) are detected between baseline and the last day of dosing in the primary study population as defined in Section 9.3, Populations for Analysis Sets.

The IA will be performed by an independent statistical support group and will be reviewed by the IDMC who will receive unblinded safety and efficacy data (see Section 10.6.6, Committees Structure). After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study (see below for details). A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making, considering the IDMC recommendation. An IDMC charter will be prepared before start of the study with more details on the IDMC and Sponsor Committee composition and organization.

Unblinded exposure response analyses will be performed by independent sponsor pharmacometricians using data available based on a predefined snapshot date at the IA, with adequate firewalls so the study team will remain blinded.

The aim of the IA at the end of Stage 1 is to assess PoC of the HDR and LDR for the primary objective. In this analysis, PoC is defined as a statistically significant reduction in the number of laboratory-confirmed DENV infections on active prophylactic dosing compared with placebo at the 20% one-sided significance level. The HDR and LDR will be tested hierarchically: First the HDR will be tested and if PoC is reached for the HDR, the LDR will be tested. Based on these results, the IDMC can advise to:

- Stop the study for futility, or
- Drop the LDR and continue the study with the placebo regimen and the HDR, or
- Continue the study with both active intervention groups (HDR and LDR) and placebo.

If the study continues, the IDMC may advise to open study recruitment to adolescent HHCs via protocol amendment.

The IDMC advice will be based on the following decision rule:

- If PoC is not reached for the HDR, the IDMC can advise to stop the study.
- If PoC is reached for the HDR but not for the LDR, the IDMC can advise to continue the study with only the HDR and placebo regimen and drop the LDR from the study.
- If PoC is reached for both HDR and LDR, the IDMC can advise to continue the study with both active intervention groups and placebo.

However, this rule is non-binding and based on a full review of all safety, efficacy, and exposure -response data available for the current study. In addition, data from other studies (eg, human challenge) may be available to guide the decision.

As the study design only allows for futility assessment at the IA, no multiplicity correction will be performed for the IA. In addition, the impact of potentially dropping the LDR at the IA on the comparison of the HDR with the placebo regimen at the FA was assessed through analytical derivation of the Type I error rate. This analysis showed the Type I error was well controlled (Type I error rate <2.5%).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ABV	alcohol-by-volume
AE	adverse event
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CPK	creatine (phospho)kinase
CRF	case report form
CV	coefficient of variation
CYD-TDV	chimeric yellow fever – dengue virus tetravalent dengue vaccine
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DENV	dengue virus
DHF	dengue hemorrhagic fever
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
DSS	dengue shock syndrome
EC_{50}	50% effective concentration
ECG	electrocardiogram
eDC	electronic Data Capture
eGFP	enhanced green fluorescent protein
ELISA	enzyme-linked immunosorbent assay
FA	final analysis
Fc	crystallizable fragment
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLDH	glutamate dehydrogenase
HCC	health care center
HCP	health care provider
HDR	high-dose JNJ-64281802 regimen
HHC	household contact
CCI	[redacted]
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent(/assent) form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product

INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LAM	lactational amenorrhea method
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry
LD	loading dose
LDH	lactate dehydrogenase
LDR	low-dose JNJ-64281802 regimen
LDL	low density lipoprotein
LLN	lower limit of laboratory normal range
MD	maintenance dose
MDR1	multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibody
NOAEL	no observed adverse effect level
NS	nonstructural protein
NSAID	nonsteroidal anti-inflammatory drug
PCC	protocol clarification communication
PCR	polymerase chain reaction
PEG400	polyethylene glycol 400
PI	principal investigator
PK	pharmacokinetic(s)
PoC	proof-of-concept
PQC	product quality complaint
PT	prothrombin time
PTT	partial thromboplastin time
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate according to Bazett's formula
QTcF	QT corrected for heart rate according to Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TOC	table of content
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of laboratory normal range
US	United States
USA	United States of America
USP	United States Pharmacopeia
VKM	viral kinetic model
WBC	white blood cell
WHO	World Health Organization
VL	viral load

Definitions of Terms

AUC_{0-24h}	area under the plasma concentration-time curve from 0 to 24 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from 0 hours to infinity
AUC_{τ}	area under the concentration curve during one dosing interval
C_{max}	maximum plasma concentration

C_{trough}	observed analyte concentration just prior to the beginning or at the end of a dosing interval
$t_{1/2}$	elimination half-life
t_{max}	time to maximum concentration

10.2. Appendix 2: Rash Management

Dengue symptomatic infection is known to result in skin rashes in most patients. Rashes may potentially also be related to the study intervention, and it may not be possible to differentiate between a rash secondary to DENV infection and one related to the study intervention. In all cases of rash that are not related to DENV infection, the below rash management should be followed.

In case a causal relationship between the rash and the study intervention 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.

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

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.

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. The skin reaction should be evaluated at the study site the same day (if possible) or the next day. Participants 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.

Grading of rash events will be based on the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS 2017).

Monitoring of the evolution of rash events will be performed as described in Table 5 below.

Table 5: Management of Rash Events by Severity Grade

	Definition	Study Intervention 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 intervention 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 and 7: 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 CRF should be completed.	Not required

	Definition	Study Intervention 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 intervention 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 CRF should be completed	Not required

	Definition	Study Intervention 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 oral body temperature ≥39.3°C to <40.0°C (≥102.7°F to <104.0°F), OR eosinophils >1,000/mm^3, 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: *Regardless* 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 CRF should be completed.	Required[c] Biopsy required within 24 hours after onset of rash.

	Definition	Study Intervention 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 2 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: *Regardless* 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 CRF should be completed.	Required[c] Biopsy required within 24 hours after onset of rash.

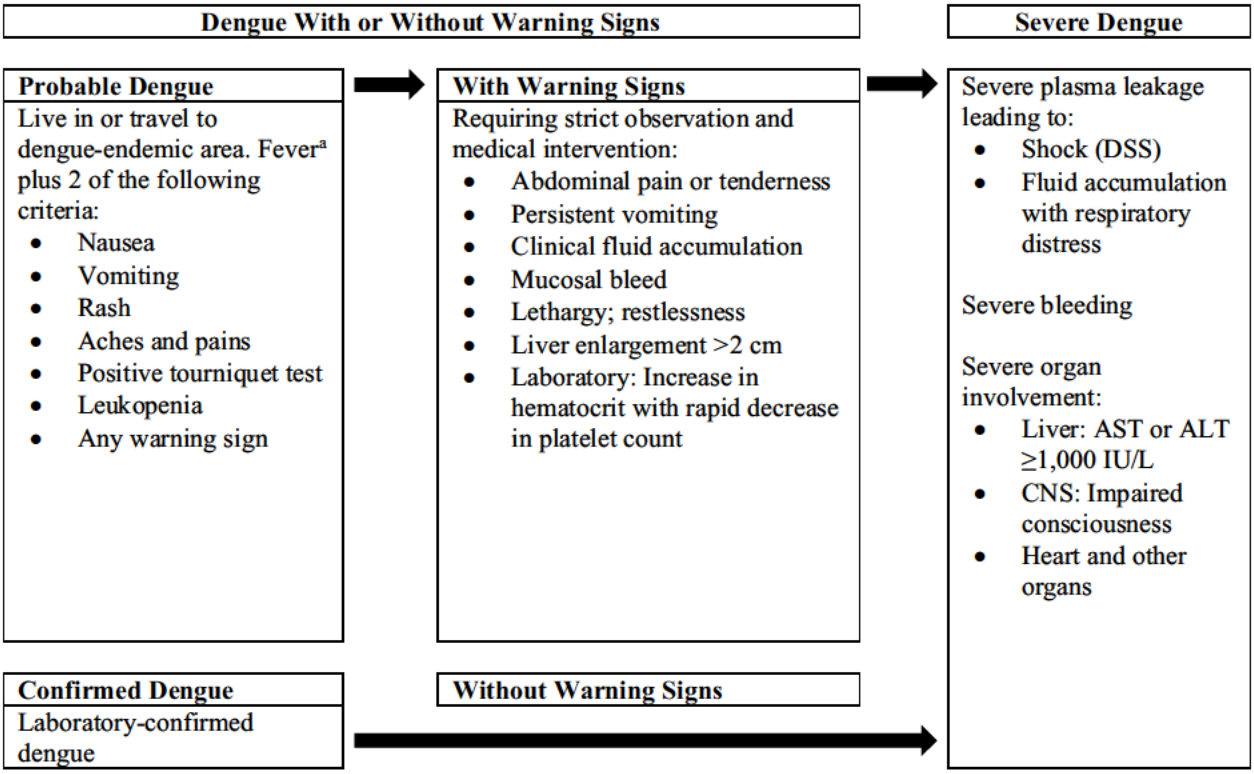
Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; IDMC = Independent Data Monitoring Committee; ULN = upper limit of normal.

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 at the study site and on the sponsor's secure server. Only the sponsor team members and the IDMC members will have access to the sponsor's secure server.
Per investigator's discretion, the participant may be treated symptomatically until the rash resolves.

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.

10.3. Appendix 3: WHO Clinical Classification of Dengue Disease



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; DSS = dengue shock syndrome
Source: Muller 2017

a. Fever is defined as an oral body temperature ≥38.0°C (104°F) confirmed by a repeat measurement at least 10 minutes after the first assessment.

10.4. Appendix 4: COVID-19 Appendix

Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the 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; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

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 or the clinical judgment 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 efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

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 COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

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 health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer 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.

Guidance Specific to This Protocol

The following emergency provisions are meant to ensure participant and staff safety while site capabilities are compromised by COVID-19-related restrictions. Remote medical consultation and alternatives to clinical laboratory assessments and study intervention administration may allow continued study participation for participants in this study.

As local restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to the original protocol conduct as soon as feasible and in accordance with any country-specific regulatory requirements.

Study Visits and Procedures

- In case **visits** to the study site are not possible, mitigations include; remote (eg, by phone/telemedicine) visits and referral of participants to health care services for safety evaluation, if deemed necessary.
- In case **assessments** cannot be performed per protocol at the study site, alternatives may be possible after discussion and agreement with the sponsor.
  - If certain assessments cannot be performed or are to be performed differently, this is to be documented in the source documents and the (electronic) CRF.
  - There are some assessments that could be conducted remotely via telephone (or videoconference). This methodology can only be used in accordance with applicable (including local) laws, regulations, guidance, and procedures. These remote assessments include review of AEs, concomitant therapy, and questions regarding general health status to fulfill any physical examination requirement.
  - All visits/assessments need to be performed by trained and delegated site staff.
  - Other procedures, eg, imaging, may be conducted at an appropriate facility.

Administration of Study Intervention

Procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at-home administration (including the potential for self-administration of study intervention) could be a possible mitigation.

Exposure to Coronavirus/Development of COVID-19

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-qPCR. This should be reported to the local health authorities as required.

In addition, the investigator needs to evaluate and discuss with the sponsor's Medical Monitor whether enrollment of a participant with acute COVID-19 infection is in line with the eligibility criteria and whether enrollment of a participant in the study is compromising the participant's safety or the data collection, quality, and interpretation. Special precaution should be taken for those who may carry a higher risk for severe COVID-19 illness.

Impact on Study Data

The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

Monitoring/Audits/Consent/Ethics

Monitoring

Depending on local restrictions, routine on-site monitoring visits may be postponed. The site monitor may set up remote visits in accordance with site and local requirements instead. Additional monitoring visits may be needed in the future to catch up on monitoring activities that can only be performed on-site.

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

Consenting and re-consenting of participants for the measures taken (including also remote consenting by phone or video consultation) will be performed as applicable and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

Ethics

In case of any protocol deviations related to COVID-19, the investigator should notify these to the local IEC/IRB/health authorities per local requirements.

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

- Participants will be allowed to receive an authorized/licensed COVID-19 vaccine throughout this study, including attenuated COVID-19 vaccines and boosters. 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 judgment 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.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.2.5, Pregnancy Testing, Section 8.3.5, Pregnancy and Appendix 7: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential

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.

  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.
- **permanently sterile (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

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 must 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 must 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.*
• Intrauterine device (IUD)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(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 must 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.*
• 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)
• Any hormonal (estrogen and/or progestogen) contraceptives (oral, injectables, implants, patches, intrauterine hormone-releasing system (IUS), etc.)[b]
• 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)
a) Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) The interaction between JNJ-64281802 and hormone-based contraceptives has not been assessed. The efficacy of hormone-based contraceptives may be decreased when coadministered with JNJ-64281802 and therefore should not be considered a highly effective contraceptive method during dosing with JNJ-64281802. A woman using any type of hormonal contraception must use an additional barrier-based contraceptive method. c) Male condom and female condom must not be used together (due to risk of failure with friction).

10.6. Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

10.6.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on 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 Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers, Clinical Trial Managers, and/or Contract Research Organizations who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with IECs/IRBs per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

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.

In situations where a departure from the protocol is unavoidable during the study, 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 research and for the corresponding ICF 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 AEs 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.

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, Study-specific Ethical Design Considerations.

10.6.2. 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.

10.6.3. Informed Consent Process and Assent Form

This study will include index cases ≥1 years of age and HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years can be included in the intervention part of the study.

When "participant" is referred to in relation to the ICF, this can be either a HHC or an index case; when "participant" is referred to in relation to the informed assent form, this refers to an index case.

Each participant, or a legally acceptable representative, must give written consent/assent 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) and assent form 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/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Informed consent or assent may be obtained remotely. Refer to the Monitoring Guideline.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants, or their legally acceptable representative, 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/assent 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, or legally acceptable representative, 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/assent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative 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/assent should be appropriately recorded by means of the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the participant.

Participants will be asked for consent/assent to provide optional samples for research (where local regulations permit). After informed consent/assent 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 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.

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

Children (minors) or participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants 7 years of age and older, depending on the institutional policies. Written assent should be obtained from participants who are able to write. A separate assent form written in language the participant can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the participant, and to the participant's parent(s) or if applicable legally acceptable representative.

See also Section 4.2.1, Study-specific Ethical Design Considerations.

10.6.4. 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/assent obtained from the participant (or his or her legally acceptable representative) includes explicit consent/assent 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, biomarker, PK, and immune 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.

10.6.5. 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 DENV infection, to understand differential intervention responders, and to develop tests/assays related to JNJ-64281802 and DENV infection. 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).

10.6.6. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis in an unblinded manner to ensure the continuing safety of the participants enrolled in this study. The committee will meet periodically to review these safety data.

This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

Any deaths, admission to the intensive care unit or severe dengue (DHF/DSS) will trigger a safety data review by the IDMC. A safety data review by the IDMC will also be triggered when the sponsor's medical monitor (or designee) judges, based on a thorough analysis of all reported ≥Grade 3 unsolicited AEs, that the study pausing criteria may have been met (see Section 7.1.3). If, in the judgment of the investigator and/or the sponsor's study-responsible physician, a significant or unexpected safety event occurs, the IDMC will review unblinded safety data. Regular safety checks will be performed by the IDMC during the course of the study.

At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or to the safety assessments to the Sponsor Committee to ensure the safety of enrolled participants. The IDMC can recommend to the Sponsor Committee to halt a dose arm or to pause or stop the study due to safety concerns.

In addition, the IDMC will review the IA data. After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study (see

Section 9.5, Interim Analysis). In case the timing of the IDMC safety review coincides with that of the scheduled IA, it may be performed as part of the IA.

Modifications recommended by the IDMC and endorsed by the Sponsor Committee will be communicated in writing to investigators, health authorities, and IEC/IRB and may be implemented without amendment to this protocol. Details will be provided in the IDMC charter.

Sponsor Committee

A Sponsor Committee will be established for the formal decision taking after IDMC recommendations on modifications to the study conduct and further continuation of the study.

The Sponsor Committee must be independent of the study conduct and include senior medical and statistical members who can make scientific and business decisions based on the IDMC recommendations.

One of the members of the Sponsor Committee will serve as the Chairperson. The Chairperson will serve as the point of contact between the IDMC and sponsor.

The roles and responsibilities of the Sponsor Committee will be detailed in the IDMC charter.

10.6.7. CCI

CCI

[redacted]

Registration of Clinical Studies and Disclosure of Results

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

10.6.8. 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, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory, PK, antiviral activity, immune, and viral genome sequencing data from the central (or local for hematology and microscopic urinalysis) laboratory into the

sponsor's database. 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.

10.6.9. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, and 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.

10.6.10. 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.

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.

10.6.11. 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/assent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; 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 other 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.

The participant's paper diary used to collect information as specified in Section 8, Study Assessments and Procedures will be considered source data.

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. These 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.

10.6.12. 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 the participant has been contacted by a regulatory agency concerning an upcoming inspection.

10.6.13. 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.

10.6.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site 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

10.7. Appendix 7: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.7.1. Adverse Event Definitions and Classification

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE 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 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 AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union 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 AE 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 AE 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 AE will be determined by whether or not it is listed in the IB for JNJ-64281802 (IB JNJ-64281802 2022).

10.7.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the investigator. The following selection must be used to assess all AEs.

Related

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

Not Related

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

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

10.7.3. Severity Criteria

An assessment of severity grade will be made using the general categorical descriptors outlined in the modified DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events supplemented with WHO toxicity grading scales in Section 10.9 and using the rash management protocol in Section 10.2.The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.7.4. 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.
- Reporting of participant pregnancy or participant partner(s) pregnancy.

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

10.7.5. Procedures

All Adverse Events

All AEs, 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 AE to study therapy. All measures required for AE 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 SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from 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 an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

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

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.7.6. Product Quality Complaint Handling

Definition

A 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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.7.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.8. Appendix 8: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory except when indicated otherwise in the table below:

Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology *To be performed locally.*	Platelet count RBC count Hemoglobin Hematocrit	<u>RBC Indices:</u> Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	<u>WBC count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A 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 *Should be performed centrally, except for baseline assessments which need to be performed both locally and centrally. Local testing at subsequent visits is at the discretion of the PI and if requested by the Sponsor.*	Sodium Potassium Chloride Blood urea nitrogen (BUN) Creatinine Glucose (nonfasting) AST/Serum glutamic-oxaloacetic ALT/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT) Lipase Amylase	Total/Direct/Indirect bilirubin Alkaline phosphatase (ALP) Creatine phosphokinase (CPK) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Low Density Lipoprotein (LDL)	

Laboratory Assessments	Parameters		
Coagulation *Should be performed centrally, except for baseline assessments which need to be performed both locally and centrally. Local testing at subsequent visits is at the discretion of the PI and if requested by the Sponsor.*	PT Activated partial thromboplastin time (aPTT) International normalized ratio (INR)		
Routine Urinalysis *Urine microscopy to be performed locally. The rest to be performed centrally. Local testing at subsequent visits is at the discretion of the PI and if requested by the Sponsor.*	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Microscopic sediment examination RBCs WBCs Epithelial cells Crystals Casts Bacteria	Quantitative protein determination
	In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.		

Laboratory Assessments	Parameters
Other Screening Tests	Urine pregnancy tests for all women, by the local laboratory: • Highly sensitive urine pregnancy testing, as indicated in the Schedule of Activities. • Additional serum or urine pregnancy tests, as determined necessary by the investigator or required by local regulation. • A urine drug screen (see Section 8, Study Assessments and Procedures for drugs to be screened) and alcohol test may be performed throughout the study at the discretion of the investigator.
Other Tests *To be performed locally and only to be performed in case the participant develops liver observations that need assessment for causality.*	• Hepatitis A IgM antibody; • HBsAgG • HBcAB • Hepatitis C RNA • Cytomegalovirus IgM antibody • Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) • Hepatitis E IgM antibody.

10.9. Appendix 9: Toxicity Grading Scale for Determining the Severity of Adverse Events

ABBREVIATIONS (used in the table)

ULN=Upper Limit of Normal

IV=Intravenous

LLN=Lower Limit of Normal

Per protocol amendment 3, the toxicity grading scale is replaced with the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 (DAIDS 2017) and supplemented with WHO toxicity grading scales where values were absent.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever[b] (°C) (°F)	37.5-to <38.6 or 99.5 to <101.5	≥38.6 to <39.3 or ≥101.5 to <102.7	≥39.3 to <40.0 or ≥102.7 to <104.0	≥40.0 or ≥104.0
Hypertension *(with the lowest reading taken after repeat testing during a visit)*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated

a Participant should be at rest for all vital sign measurements.

b Oral temperature: after no recent hot or cold beverages or smoking.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/Vomiting	Transient (< 24 hours) or intermittent AND no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Diarrhea	Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Fatigue or Malaise Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Myalgia	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Rash[a] **Specify type, if applicable**	Localized rash that is easily tolerated and/or may require one dose of medication	Diffuse, maculopapular rash, or target lesions. Symptomatic (pain/pruritus) but does not interfere with function and/or requires more than one dose of medication	Diffuse rash AND vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	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

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life -threatening (Grade 4)
Illness or clinical adverse event not identified elsewhere in the grading table.	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

a Please refer to Section 10.2 for the rash management protocol details.

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.

Biochemistry[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium - Hyponatremia mEq/L	130 to < 135	125 to < 130	121 to < 125	≤ 120
Sodium - Hypernatremia mEq/L	146 to < 150	150 to < 154	154 to < 160	≥ 160
Potassium - Hyperkalemia mEq/L	5.6 to < 6.0	6.0 to < 6.5	6.5 to < 7.0	≥ 7.0
Potassium - Hypokalemia mEq/L	3.0 to < 3.4	2.5 to < 3.0	2.0 to < 2.5	< 2.0
Glucose - Hypoglycemia mg/dL	55 to 64	40 to < 55	30 to < 40	< 30
Glucose **Fasting mg/dL** **Non-Fasting - mg/dL**	110 to 125 116 to 160	> 125 to 250 > 160 to 250	> 250 to 500 > 250 to 500	≥ 500 ≥ 500
Uric Acid mg/dl	7.5 to <10.0 mg/dL	10.0 to <12.0 mg/dL	12.0 to <15.0 mg/dL	≥15.0 mg/dL
Blood Urea Nitrogen (BUN) increase by factor	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Creatinine	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN	> 1.8 to < 3.5 x ULN	≥ 3.5 x ULN
Calcium - hypocalcemia mg/dL	7.8 to < 8.4	7.0 to < 7.8	6.1 to < 7.0	< 6.1
Calcium - hypercalcemia mg/dL	10.6 to < 11.5	11.5 to < 12.5	12.5 to < 13.5	≥ 13.5
Magnesium - hypomagnesemia mEq/l	1.2 to < 1.4	0.9 to < 1.2	0.6 to < 0.9	< 0.6
Phosphorous - hypophosphatemia mg/dL	2.0 to < LLN	1.4 to < 2.0	1.0 to < 1.4	< 1.0
Creatine (phospho)kinase (CPK)	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Albumin - Hypoalbuminemia g/dL	3.0 to < LLN	≥ 2.0 to < 3.0	< 2.0	--
Alkaline phosphate High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Gamma-glutamyltransferase GGT	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
AST increase by factor	1.1 to 2.5x ULN	2.6 to 5.0x ULN	5.1 to 10x ULN	> 10x ULN
ALT increase by factor	1.1to- 2.5x ULN	2.6 to 5.0x ULN	5.1 to 10x ULN	> 10x ULN
Total Bilirubin	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Total Cholesterol mg/dl **≥ 18 years of age**	200 to < 240	240 to < 300	≥ 300	NA
< 18 years of age	170 to < 200	200 to < 300	≥ 300	NA
LDL, Fasting, High **≥ 18 years of age**	130 to < 160 mg/dL	160 to < 190mg/dL	≥ 190mg/dL	N/A
LDL, Fasting, High **< 18 years of age**	110 to < 130mg/dL	130 to < 190mg/dL	≥ 190 mg/dL	N/A
Triglycerides, Fasting, High	150 to 300mg/dL	>300 to 500mg/dL	>500 to <1000md/dL	> 1000mg/dL
Lipase	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Amylase	1.1-1.5x 1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

[a] 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.

Hematology[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)

Hemoglobin (Female) - gm/dL	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
Hemoglobin (Male) - gm/dL	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
WBC Decrease - cell/mm3	2,000 to 2,499	1,500 to 1,999	1,000 to 1,499	< 1,000
Lymphocytes Decrease - cell/mm3	600 to < 650	500 to < 600	350 to < 500	< 350
Neutrophils Decrease - cell/mm3	800 to 1,000	600 to 799	400 to 599	< 400
Platelets Decrease - cell/mm3	100,000 to < 125,000	50,000 to < 100,000	25,000 to < 50,000	< 25,000
PT - increase by factor (prothrombin time)	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
aPTT - increase by factor (activated partial thromboplastin time)	≥1.01 to ≤1.66 x ULN	>1.66 to ≤2.33 x ULN	>2.33 to ≤3.00 x ULN	>3.00 x ULN
Fibrinogen decrease - mg/dL	100 to < 200	75 to < 100	50 to < 75	< 50
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN

[a] 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[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Protein	1+	2+	3+ or higher	Hospitalization or dialysis
Glucose	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	Hospitalization for Hyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Hospitalization or packed red blood cells (PRBC) transfusion

[a] 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.

10.10. Appendix 10: Examples of Disallowed Medications

Please note that the below list is not a definitive list of disallowed medications, investigators are advised to ensure any medications being prescribed are not metabolized by the prohibited enzymatic pathways.

Strong CYP3A4 inhibitors

Amiodarone	Idelalisimib	Posaconazole
Ceritinib	Itraconazole	Ribociclib
Clarithromycin	Lonafarnib	Ritonavir
Cobicistat	Methimazole	Stiripetol
Danazol	Midostaurin	Telithromycin
Delavirdine	Nefazodone	Troleandomycin
Ditiocarb	Nelfinavir	Voriconazole
Econazole	Nilotinib	

Strong CYP3A4 inducers

Apalutamide	Lumacaftor/Ivacaftor	Rifampin
Carbamazepine	Mitotane	St. John's wort (*Hypericum perforatum*)
Enzalutamide	Phenobarbital	
Ivosidenib	Phenytoin	

CYP3A4 substrates with a narrow therapeutic index

Benzodiazepines (eg, clonazepam, midazolam, triazolam)
Chemotherapeutic agents
Ergot derivatives
Opioids (eg, fentanyl, hydrocodone)

Bosentan	Flecainide	Tacrolimus
Clopidogrel	Ivabradine	Tadalafil
Clozapine	Lurasidone	Temsirolimus
Cyclosporine	Pimozide	Tianeptine
Digoxin	Primidone	Tolvaptan
Disopyramide	Propafenone	Vardenafil
Dofetilide	Quinidine	Voclosporin
Eplerenone	Sildenafil	Warfarin
Everolimus		

Sensitive BCRP substrates

Folic acid	Pravastatin	

Anticoagulants

Apixiban	Heparin	Warfarin
Dabigatran	Rivaroxaban	

NSAIDs

Celexocib	Ibuprofen	Naproxen
Diclofenac	Indomethacin	Piroxicam

Corticosteroids (systemic[a])

Cortisone	Methylprednisolone	Prednisolone
Dexamethasone	Prednisone	

a Topical administration is allowed.

10.11. Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments

10.11.1. Stopping Criteria

10.11.1.1. ALT or AST

Liver Chemistry Stopping Criteria
ALT or AST- ≥5xULN, or
ALT or AST- ≥3xULN persists for ≥4 weeks, or
ALT or AST- ≥3xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome), or
ALT or AST- ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured, or
ALT or AST- ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Dengue infection can alter/increase liver enzymes in the infected individual. For this reason, if any of the above liver chemistry stopping criteria are met, investigator together with sponsor will decide on the discontinuation of the study intervention. If a participant is discontinued, they will not be restarted or rechallenged again.

10.11.2. Follow-up Assessments

- **Repeat testing** to confirm laboratory abnormalities within 24 hours prior to stopping, unless safety is considered at risk by the sponsor and/or investigator
- Report the event to the sponsor **within 24 hours to decide on discontinuing study intervention**

10.11.2.1. Liver Follow-up Assessments with discontinued Study Intervention

If liver chemistry stopping are deemed to be possibly related to the drug intervention by the investigator and sponsor, the below monitoring and follow up assessments apply:

Suggested Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments[f]**
• Complete the CRF according to CRF completion guidelines, and complete an SAE data collection tool if the event also met the criteria for an SAE[b] • Perform follow-up assessments as described in the Follow Up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**)	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis after the most recent dose[e] • Obtain serum CPK, lactate dehydrogenase (LDH), GGT,

MONITORING:

If ALP <2 x ULN, ALT or AST- ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):

- Repeat liver chemistry tests (include ALT, AST, ALP, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours**
- Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline
- A specialist or hepatology consultation is recommended

If ALT or AST- ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:

- Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours**
- Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline

glutamate dehydrogenase (GLDH), and serum albumin

- Fractionate bilirubin
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF as per CRF completion guidelines
- Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications)
- Record alcohol use on the CRF as per CRF completion guidelines

If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured) obtain the following in addition to the assessments listed above**:**

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins
- Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week
- Depending on availability, liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete CRF as per CRF completion guidelines
- Liver biopsy may be considered and discussed with local specialist if available:
  - In participants when serology raises the possibility of autoimmune hepatitis (AIH)

	– In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In with acute or chronic atypical presentation • If liver biopsy conducted complete CRF as per CRF completion guidelines

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN and total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALP <2 x ULN, ALT or AST ≥3 x ULN and total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or ALP <2 x ULN , ALT or AST ≥3 x ULN and INR >1.5 (if measured) may indicate severe liver injury (possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met (excluding studies of hepatic impairment or cirrhosis). The INR stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

[d] Includes: hepatitis A IgM antibody; HBsAgG and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] PK sample may not be required for participants. record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

[f] Local laboratories can perform the follow-up assessments where available to allow a rapid turnaround in these assessments.

10.11.2.2. Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criterion and Actions with Continued Study Intervention	
Criterion	**Actions**
ALT or AST- ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR<1.5 (if measured)**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor within **24 hours** of learning of the abnormality to discuss participant safety PARTICIPANT CAN CONTINUE STUDY INTERVENTION. • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize or return to baseline

	• If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 10.11.2.1 Liver Follow-up Assessments • If, after 4 weeks of monitoring, ALT or AST - <3xULN and total bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

10.12. Appendix 12: Protocol Amendment History

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

Amendment 2 (2 December 2022)

Overall Rationale for the Amendment: The main purpose of this amendment is to implement regulatory feedback with regards to study pausing in case of safety concerns. In addition, it was clarified that participants with certain laboratory abnormalities at baseline (Day 1) will be discontinued from study intervention. Serum lipase was added to the blood chemistry panel and a clarification concerning the recording of body temperature was added.

The changes made to the clinical protocol 64281802DNG2004 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
7.1.2 Study Pausing Criteria; 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.6.6 Committees Structure	Study pausing criteria were added. The sponsor's medical monitor (or designee) will do a thorough analysis of all reported ≥Grade 3 unsolicited AEs to determine whether a safety data review by the IDMC is warranted. If the IDMC judges that the study pausing criteria have been met, the IDMC will recommend to either pause the study or to implement modifications to the study conduct and/or to the safety assessments. In addition, it was clarified that the investigator should notify the sponsor's medical monitor (or designee) immediately and no later than 24 hours after becoming aware of any ≥Grade 3 unsolicited AE considered related to study intervention.	Upon Health Authority request
7.1 Discontinuation of Study Intervention	It was clarified that participants who report with 2 or more ≥Grade 2 laboratory abnormalities for elevations of triglycerides, low-density lipoprotein cholesterol, and/or total cholesterol, and/or 2 or more ≥Grade 2 laboratory abnormalities for other laboratory parameters at baseline (Day 1) will be discontinued from study intervention.	To ensure that participants with clinically significant laboratory abnormalities at baseline discontinue treatment with study intervention.
10.8 Appendix 8: Clinical Laboratory Tests	Serum lipase will be monitored during the dosing and follow-up phases.	Upon Health Authority request
1.3.2.2 Double-blind Prophylactic Dosing: Day 1 to Day 13; 1.3.2.3 Double-blind Prophylactic Dosing (Day 14 to Day 28) and Follow-up Phase; 8 STUDY ASSESSMENTS AND PROCEDURES;	It was clarified that body temperature will be recorded by the participant in a diary daily (preferably at the same time each day) and in case of feeling feverish, and that it will be added to the CRF by study site personnel only in case the body temperature is ≥37.5°C (99.5°F).	Clarification

Section number and Name	Description of Change	Brief Rationale
8.2.2 Vital Signs		
Throughout the protocol	Minor grammatical, formatting, or spelling changes and clarifications were made.	Minor errors were corrected.

Amendment 1 (04 October 2022)

Overall Rationale for the Amendment: The main purpose of this amendment is to remove serology as a criterion for identifying dengue virus (DENV) infection in household contacts (HHC) for the evaluation of the prophylactic effect of JNJ-64281802 for the primary endpoint. In addition, the measurement of anti-DENV antibodies was moved from a secondary to an exploratory endpoint. Other changes in this amendment include the following:

- The diagnosis of DENV infection in index cases was clarified, and the possibility of using anti-DENV IgM test if necessary was added.
- The follow-up period was extended to 62 days following the last dose.
- The calculation of the prophylactic efficacy was adjusted.
- The requirement to have energy bars along with the study intervention was removed.
- The other changes, such as performing clinical laboratory analyses in local laboratories, were made for logistical reasons.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis: Hypothesis; primary endpoint; 9.1 Statistical Hypotheses; 9.4.2 Primary Endpoint(s)	- Removed serology as a criterion for identifying laboratory-confirmed DENV infection in HHC. - Specified the definition of laboratory-confirmed DENV infection.	- To restrict the identification of lab-confirmed DENV infection to detection of the DENV virus itself (either viral RNA and/or NS1 antigen) as detection of anti-DENV antibodies can be hampered by many variable factors such as cross reactivity with other flaviviruses. - To clarify what is meant by laboratory-confirmed DENV infection.
1.1 Synopsis: Objectives and Endpoints; Statistical Methods; 3 OBJECTIVES AND ENDPOINTS	Measurement of anti-DENV antibodies was moved from a secondary objective to an exploratory objective.	As the detection of anti-DENV antibodies can be hampered by many variable factors, this analysis was moved to exploratory objective.
1.1 Synopsis: Objectives and Endpoints; 3 OBJECTIVES AND ENDPOINTS	Removal of the analysis of neutralizing antibodies as an exploratory objective. It will be analyzed in an exploratory research.	Detection of neutralizing antibodies can be hampered by many variables.
1.1 Synopsis; 1.3.1 Index Cases; 4.1 Overall Design; 5.1 Inclusion Criteria 8.7.1 NS1 Rapid Test and RT-PCR of Index Cases	The criteria for identifying index cases were modified to include the possibility of using anti-DENV IgM test.	To allow for the possibility to use an alternative anti-DENV IgM test when a DENV NS1 or DENV PCR test is not available.
1.3.2.2 Double-blind Prophylactic Dosing: Day 1 to Day 13; 1.3.2.3 Double-blind Prophylactic Dosing (Day 14 to Day 28) and Follow-up Phase	Blood samples should be taken prior to the first drug intake only on Day 1.	Day 1 predose blood sample required as baseline sample, other sampling points can be done at any time points of the visit day to facilitate operational conduct of the trial.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis: Overall Design - Follow-up Phase; 1.3.2.3 Double-blind Prophylactic Dosing (Day 14 to Day 28) and Follow-up Phase; 4.1 Overall Design Follow-up Phase; 4.4 End of Study Definition Study Completion Definition; 8 STUDY ASSESSMENTS AND PROCEDURES	- A follow-up visit and immune assessments on Day 90, and phone follow-ups between Day 50 and Day 90 were added. - The approximate duration of the study was changed from 7 weeks to 13 weeks to reflect the additional follow-up. - Clarified in footnote that concomitant medications and AEs will be reviewed throughout the follow-up period until Day 90.	To assess post-treatment DENV serology and to document and review any cases of symptomatic dengue during an extended follow-up period.
1.3.2.3 Double-blind Prophylactic Dosing (Day 14 to Day 28) and Follow-up Phase	- Specified that participants showing signs or symptoms of DENV infection between Day 28 and Day 90 had to come to the study site. - Specified that after Day 28 the occurrence of AEs will be based on phone monitoring in addition to the site visits on Days 40, 50, and 90. - Added a window of +/- 1 day to the Day 28 visit.	- To ensure that blood would be drawn for antiviral activity assessment and viral sequencing for infections that occur after the last dose. - To ensure safety is regularly monitored between participants' site visits. - To allow for the Day 28 blood sampling to occur on a Monday in case Day 28 is a Sunday.
1.2 Schema Figure 1: Schematic Overview of the Study	The number of days between the end of treatment and follow-up was modified.	To account for the additional Day 90 follow-up.
1.1 Synopsis: Description of Intervention; 1.3.2.2 Double-blind Prophylactic Dosing: Day 1 to Day 13; 4.3 Justification for Dose 6.1 Study Intervention(s) Administered; Table 2; 8 STUDY ASSESSMENTS AND PROCEDURES	The requirement to have an energy bar was removed.	The impact of additional energy on bioavailability was minimal based on data from the relative bioavailability study 64281802DNG1006.
2.2 Background	An additional result from Part 2 of study 64281802DNG1006 was added.	To explain why energy bars were no longer required with dosing.
6.8 Concomitant Therapy	- Domperidone was removed from the list of concomitant medications that are not allowed. - Concomitant medications that are prohibited were updated.	Newly collected information on JNJ-64281802 as an inhibitor and inducer of various CYP enzymes and transporter proteins obtained in Study DNG1005 has led to the revision of disallowed concomitant medication.
2.2 Background; 2.3.1 Risks for Study Participation	Summary of study 64281802DNG1004 was added. The safe doses were updated based on study 64281802DNG1004.	For completeness since the final 64281802DNG1004study report became available.
2.2 Background Study DNG1001	In the Background section, the safety summary of Study 64281802DNG1001 was modified for consistency with the text in other documents.	For consistency with other Phase 2 protocols and the Investigator's Brochure.

Section number and Name	Description of Change	Brief Rationale
1.3.2.3 Double-blind Prophylactic Dosing (Day 14 to Day 28) and Follow-up Phase	An additional pregnancy test was added on Day 28.	To increase the likelihood of detecting a pregnancy while on the study intervention.
1.1 Synopsis: Statistical Methods; 9.4.4.1 Safety Analyses 10.2 Appendix 2: Rash Management	Rash was added as an event that requires narrative reporting. Clarified that rashes are to be assessed by investigators at their discretion. All rashes that are not related to DENV infection are to undergo rash management assessment.	To generate more comprehensive clinical data and better assess rashes that are not related to dengue infection.
1.1 Synopsis: Statistical Methods; 9.4.2 Primary Endpoint(s)	- Clarified the calculation of prophylactic efficacy: The odds-ratio from the logistic regression model will be used to estimate prophylactic efficacy. - The statement referring to interim analysis in the sensitivity analysis was deleted.	- Given the expected low incidence, the odds ratio will be a very good approximation of the relative risk. - The reference to the Interim Analysis section is not needed as no sensitivity estimators are planned for the interim analysis.
1.1 Synopsis: Statistical Methods; 4.1 Overall Design; 9.2 Sample Size Determination	The number of participants expected to be enrolled was updated from 1,300–1,850 to 1,250–1,850.	The number of expected participants was recalculated.
10.6.8 Data Quality Assurance; 10.8 Appendix 8: Clinical Laboratory Tests	- Clarification made that hematology and microscopic urinalysis must be performed by local laboratories and results entered by the clinical site staff. - Lactose dehydrogenase (LDH) and bicarbonate were removed from the list of analytes for clinical chemistry.	- For protocols performed in remote settings, sample shipment times can exceed the specimen viability time, and central laboratory analysis cannot be performed due to sample degradation. This directly impacts monitoring of participant safety. Therefore, for perishable samples, hematology testing and microscopic urinalysis will be performed locally. - Analysis of LDH and bicarbonate were not deemed medically necessary for the analysis and assessment of safety for this study.
8 STUDY ASSESSMENTS AND PROCEDURES Overview; 10.8 Appendix 8: Clinical Laboratory Tests	Alcohol test was kept general and not limited to a breath test.	Some study sites do not use alcohol breath test.
1.1 Synopsis: Number of participants; 5.1 Inclusion Criteria	The maximum body mass index in the inclusion criteria was increased from 33 to 35.	To reduce screen failures due to BMI. No implications for safety are expected.

Section number and Name	Description of Change	Brief Rationale
2.3.1 Risks for Study Participation; 5.2 Exclusion Criteria; 6.8 Concomitant Therapy 10.4 Appendix 4: COVID 19 Appendix	- The vaccination exclusion criterion was modified so that it excluded attenuated COVID-19 vaccination. - Clarification regarding COVID-19 vaccinations in the exclusion criteria.	- To allow for vaccination against COVID-19. - Attenuated COVID-19 vaccines and boosters (if these become available during the study) were included in the exclusion criteria since information on the type of vaccine (live or non-live attenuated) taken may not be readily available. Once the study intervention has stopped, receiving COVID-19 vaccination is up to the discretion of the investigator.
1.1 Synopsis: Objectives and Endpoints; 3 OBJECTIVES AND ENDPOINTS	Modification of the exploratory endpoints.	The exploratory endpoints were phrased more precisely.
1.1 Synopsis: Objectives and Endpoints; 3 OBJECTIVES AND ENDPOINTS	Removal of the exploratory objective to evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of laboratory-confirmed DENV infection up to Day 50 among HHC who have no evidence of current DENV infection at baseline and who completed study intervention.	Laboratory-confirmed DENV infection is defined as a positive result on the DENV RNA and/or DENV NS1 protein assay. In order not to miss the detection of a laboratory-confirmed DENV infection, at least twice weekly sampling is necessary, which is only planned up to Day 28.
1.1 Synopsis: Description of Study Intervention; Table 2	CCI [redacted]	CCI [redacted]
1.3.2.4 Discontinuation From Study Intervention or Study; 7.1 Discontinuation of Study Intervention	Addition that immune assessments, viral analysis, and viral sequencing will be performed at withdrawal and follow-up visits when participant discontinues from the study or study intervention.	Sequencing at these time point added (consistent with other sampling time points) to characterize DENV variants associated with resistance to JNJ-64281802.
1.3.2.4 Discontinuation From Study Intervention or Study	- Clarified that upon the visit at discontinuation, participants will come to the study site. - Added footnote (d) - Modified the description of the follow-up visit (removed “Safety” and made clarifications in footnote d)	- Since ECG measurements will have to be taken, the withdrawal visit needs to be at the study site. - To specify that safety assessments and clinical laboratory tests at follow-up will be performed at the discretion of investigators. - To clarify that the follow-up visit is performed mainly for antiviral and immune assessments. No safety issues are expected.

Section number and Name	Description of Change	Brief Rationale
1.3.2.5 Pharmacokinetic Substudy; 6.4 Study Intervention Compliance; 8 STUDY ASSESSMENTS AND PROCEDURES Sample Collection and Handling	- Requirement for study site visit on Days 29 and 32 in the PK Substudy was made optional. - The requirement to visit study site on Days 2 and 3 was specified in the footnote.	- Visit can be performed at the site or at home. - To maintain consistency with the table.
7.2.1 Withdrawal From the Use of Research Samples	Clarified that the only optional research samples are for pharmacogenomics.	To clarify that the only optional samples are for pharmacogenomics.
1.1 Synopsis: Safety Analysis 1.3.2.2 Double-blind Prophylactic Dosing: Day 1 to Day 13; 1.3.2.3 Double-blind Prophylactic Dosing (Day 14 to Day 28) and Follow-up Phase; 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.2 Vital Signs	- Removed body temperature from vital signs. - Specified that body temperature needs to be recorded only in case of fever.	To clarify that normal body temperature does not need to be recorded.
5.2 Exclusion Criteria	Removed the specification that constipation is considered as an exclusion criterion if it lasts >2 days.	To consider any occurrence of constipation as an exclusion criterion.
6.7 Treatment of Overdose	The option for the decision to be taken in case of overdose was changed to continue (or discontinue) study intervention.	No study treatment interruption or modification is allowed in the study.
Throughout the protocol	Minor grammatical, formatting, or spelling changes and clarifications were made.	Minor errors were corrected, and clarifications added.

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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	19-Jul-2023 05:12:57 (GMT)	Document Approval