Janssen Research & Development

Statistical Analysis Plan

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

Protocol 64281802DNG2004; Phase 2

JNJ-64281802 (Monsnodenvir)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table [xx] – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	21 October 2024	Not Applicable	Initial release

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the analysis of efficacy and safety of study drug JNJ-64281802. A separate document, the data presentation specifications (DPS), for mock shells and a table of contents for tables, figures and listings is also produced. The SAP is to be interpreted in conjunction with the protocol[1](amendment 3).

The study was prematurely ended on 02 October 2024 when 21 laboratory confirmed dengue infections between baseline and last day of dosing (+1 day) were observed in the primary analysis population and 14 symptomatic dengue infection between baseline and last day of dosing (+1 day) were observed in the complete study population. This decision was taken by Johnson & Johnson based on portfolio reprioritization and was not based on any safety concerns. The current SAP will cover the final analysis (FA). Changes to the per protocol planned analysis are described in section 6.2, Appendix 2.

1.1. Objectives and Endpoints

The primary, secondary and exploratory objectives and endpoints covered in this SAP are listed below.

Objectives	Endpoints
Primary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of laboratory-confirmed DENV infection among household contacts (HHCs) who have no evidence of current DENV infection at baseline.	• Laboratory-confirmed DENV infection[a] between baseline and the last day of dosing + 1 day.
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 (see Safety Evaluations section) among all HHCs.	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing + 1 day.
Secondary	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection through development of signs and symptoms (see Safety Evaluations section) among HHCs who have no evidence of current DENV infection at baseline.	• Laboratory-confirmed symptomatic DENV infection[b] between baseline and the last day of dosing + 1 day.
• To assess the safety and tolerability of 2 dose regimens (high and low) of JNJ-64281802 among HHCs.	• 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.

Objectives	Endpoints
• To assess the pharmacokinetics (PK) of JNJ-64281802 following repeated oral dosing among HHCs.	• Observed analyte concentrations over time.
Exploratory	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection as measured through increase of anti-DENV antibodies among HHCs who have no evidence of current DENV infection at baseline.	• Increase in anti-DENV antibodies between baseline and Day 40. • Increase in anti-DENV antibodies between baseline and Day 50. • Increase in anti-DENV antibodies between baseline and Day 90.
• To identify circulating DENV serotypes/genotypes and genetic variants among index cases and HHCs.	• 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 HCC using index case sequence as reference.

AE = adverse event; DENV = dengue virus; ECG = electrocardiogram; HHC=household contact; RNA=ribonucleic acid; NS = non-structural protein; PCR = polymerase chain reaction; SAE = serious adverse event.

[a] 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 days time window around the positive PCR or NS1 test.

The statistical analysis for the following exploratory objectives might be performed, but will depend on the unblinded results of the primary and secondary endpoints, for hypothesis generating purposes:

Objectives	Endpoints
Exploratory	
• To evaluate the prophylactic effect of JNJ-64281802 with respect to reduction of DENV RNA among enrolled HHCs who have no evidence of current DENV infection at baseline and who are infected post baseline.	• The maximum DENV RNA levels between baseline and the last day of dosing + 1 day.
• To evaluate the antiviral effect of JNJ-64281802 as early treatment among HHCs who have evidence of DENV infection at baseline.	• Time to end of detectable DENV RNA and/or reduction in DENV RNA load. • DENV-associated signs and symptoms.

HYPOTHESIS

See Section 2, Statistical Hypotheses.

1.2. Study Design

Study 64281802DNG2004 (further referred to as DNG2004) is Phase 2 randomized, double-blind, placebo-controlled, double-dummy, multicenter, interventional trial with an event-driven design that will evaluate the prophylactic efficacy (PE) and safety of 2 dose regimens of JNJ-64281802 for the prevention of dengue infection in HHCs of a DENV-infected index case.

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 in dengue-post 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.

There are 4 sequential phases in the study: DENV-infected index case identification, screening of the household contacts (HHCs) of the index case, double-blind prophylactic dosing, and the follow-up phase.

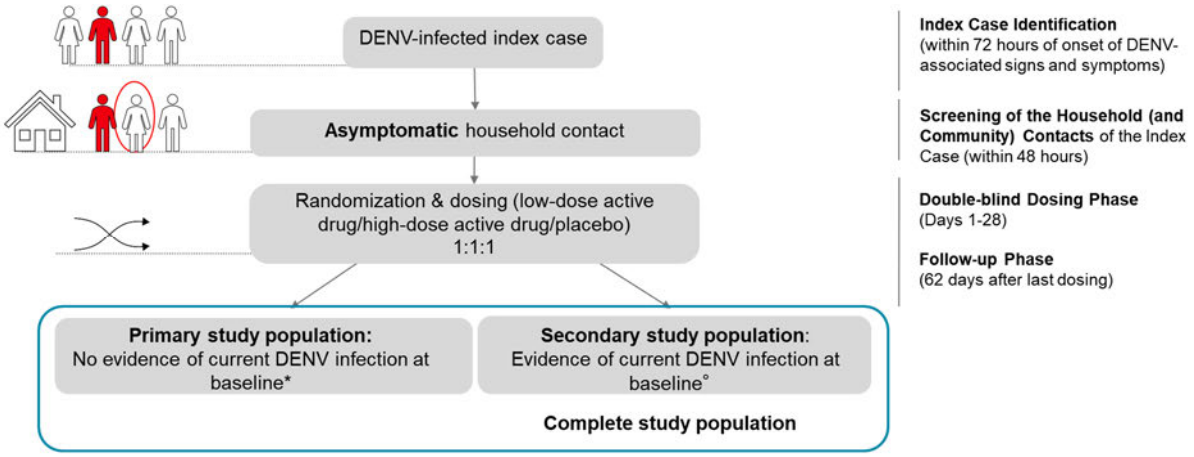
The study included index cases ≥1 years of age who participated for one visit only, and HHCs aged 16 or 18 (depending on the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years who were included in the intervention part of the study.

An index case is a patient (≥1 years old) with laboratory-confirmed dengue identified in the community (ie, hospital and/or health care center/health care provider). If the index case was 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) was obtained. After informed consent/assent was obtained from the patient or from the legal guardian(s), a blood sample for viral assessments was collected, and the person's HHCs were contacted.

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, during early morning hours or twilight hours). HHCs had to be asymptomatic at screening and could 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 on samples taken at baseline.

Participants (ie. HHCs) were randomized in a 1:1:1 ratio to receive the study intervention as high dose regimen (HDR), low dose regimen (LDR), or as matching placebo in a double-dummy fashion. The study used randomization at the individual participant level. Participants were 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 was balanced by using randomly permuted blocks and was stratified by country. A separate randomization list was created for the PK substudy.

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

The interactive web response system (IWRS) assigned a unique intervention code, which dictated the intervention assignment and matching study intervention kit for the participant. 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.

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to prevention of laboratory-confirmed DENV infection (further referred to as DENV infection) from baseline until the last day of dosing + 1 day in study participants who are DENV RNA and NS1 protein negative at baseline (further referred to as the primary analysis population). DENV infection will be measured by a positive result on a DENV RNA assay and/or a DENV NS1 protein assay.

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

The IA was scheduled when 24 DENV infections were observed in the primary analysis population. All HHCs with an enrollment date before or at the date of this 24th laboratory confirmed DENV infection would be included in the IA. The IA data base should have been

cleaned and locked and should have contained all data of the included HHCs that is needed to derive the primary endpoint, all PK data and all safety and tolerability data up to their last day of dosing (day 28 or earlier, in case of discontinuation) + 1 day.

Based on the results from the IA and other available information from other studies (eg, human challenge), the LDR could be dropped in Stage 2.

Unless stopped for futility at the IA, the study would continue till 36 DENV infections were observed in the primary study population and 24 symptomatic DENV infections were observed in the complete study population. Symptomatic DENV infections are defined as having at least 2 solicited systemic AEs (see protocol[1]), 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 days' time window around the positive PCR or NS1 test, between baseline and the last day of dosing + 1 day. Both conditions on DENV infections and symptomatic DENV infections needed to be satisfied before recruitment was considered complete.

The study was prematurely ended before the IA on 02 October 2024 due to portfolio reprioritization., therefore no IA is performed and the analysis after this premature end will be considered as FA. This decision was not based on any safety concerns.

2. 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 from baseline until the last day of dosing + 1 day 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 a DENV NS1 protein (ELISA) test result. The primary efficacy endpoint is the presence or absence of a laboratory-confirmed DENV infection between baseline and the last day of dosing + 1 day. The primary analysis population consists of study participants who are DENV RNA and NS1 protein negative at baseline. The null hypothesis is that the DENV infection rate from baseline until the last day of dosing + 1 day in the primary analysis population is at least as high in participants on prophylactic dosing with JNJ-64281802 than in participants on placebo.

3. SAMPLE SIZE DETERMINATION

The study is an event-driven design where study recruitment would continue until the required number of events was reached. Unless stopped for futility at the IA, the study would continue till 36 DENV infections were observed in the primary study population and 24 symptomatic DENV infections were observed in the complete study population (see Section 4, Populations for Analysis). Both conditions needed to be satisfied before recruitment could be considered complete. An IA for PoC was planned when 24 DENV infections were observed in the primary study population. The targets of 24/36 DENV infection events in the primary study population and 24 symptomatic DENV in the complete study population were determined through simulation based on the following requirements and assumptions.

Requirements

- at the IA 90% power is required, using a 20% one-sided significance level, to obtain PoC on the primary endpoint (DENV infections in the primary study population) for HDR and LDR if they reach the target PE of 75%;
- at the FA 80% power is required, using a 2.5% one-sided significance level, to test the primary hypothesis of the study for HDR and LDR if they reach the target PE of 75%;
- in addition, at the FA, 80% power is required, using a 20% one-sided significance level, for PoC for the key secondary endpoint (symptomatic DENV infections in the complete study population) if at least HDR reaches the target PE against symptomatic DENV infection of 72.5%;

Assumptions

- the number of eligible and recruited HHC per index case was hypothesized to be 1.5;
- the proportion of unevaluable subjects (drop-outs, missing data) was hypothesized to be 20%;
- the proportion of recruited HHC NS1+ and/or PCR+ at recruitment was hypothesized to be 20%;
- the incidence of DENV infection events in the primary study population was hypothesized to be 7.5% during the 28-day dosing period. This assumption is based on the 15 to 18% incidence of DENV infection in Nha Thrang (unpublished data), Vietnam, as observed during an epidemiologic study of HHCs using seroconversion over a 1-month period after identification of the index case. An incidence of ~50% of the observed seroconversion rate was assumed to cover variations in incidence rates across sites and countries and to allow for potential false positive seroconversion results;
- the proportion of incident DENV infections that become symptomatic in the primary study population was hypothesized to be 20% during the 28-day dosing period;
- the proportion of prevalent DENV infections that become symptomatic in the secondary study population was hypothesized to be 10% during the 28-day dosing period.

The simulations are fully described in the modelling and simulation report (MSR)[2], which also contains the simulation programs.

The simulations showed that at the FA and under the protocol assumptions, the study design results in at least 85% power for the primary objective assessed for the HDR and at least 80% power for the key secondary analysis, irrespective of the PE LDR. If the PE LDR is at least 90% of the PE HDR, the study also has at least 80% power for the primary objective assessed for the LDR and has at least 90% power for the key secondary objective. The expected recruitment of the study ranges from 1250 (assuming the PE of LDR is 0%) to 1850 (assuming the PE of LDR is equal to the PE of HDR, ie. 75%). If the PE of LDR is 50% of the PE of HDR, the expected study recruitment is 1455. If 1.5 eligible HHC can be recruited/index case, this requires the identification of nearly 1000 index cases

The study design is robust to minor deviations from the protocol assumption. If the PE of HDR is 5 percentage points lower than the protocol assumptions, the power for the primary analysis (HDR) is maintained to ≥77%. If the incidence or prevalence of (symptomatic) DENV infections is different from protocol assumptions, the proposed design generally maintains a power for the primary analysis ≥80% and for the key secondary analysis ≥75%. However, if incidence of (symptomatic) DENV infections is lower than expected the total study recruitment will be increased.

The study ended prematurely when 21 laboratory confirmed dengue infections between baseline and last day of dosing (+1 day) were observed in the primary analysis population and 14 symptomatic dengue infection between baseline and last day of dosing (+1 day) were observed in the completed study population.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants (index cases and HHCs) who sign the ICF.
Index Case population	All participants enrolled as an index case, with a laboratory-confirmed DENV infection. Test results of a NS1 rapid test and/or RT-PCR test that were performed outside the study by local standard-of care ≤72 hours of screening may be used to confirm the 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, who had no evidence of current DENV infection at baseline (based on target not detected (TND) results for DENV RNA assay and, if available, a negative/borderline result for NS1 protein assays) and with at least 1 result for DENV RNA or NS1 protein assay available post baseline up to and including the last day of dosing + 1 day 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 at baseline) 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 participants included in the primary or secondary study population. 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. This population will be used to the assess the plasma concentrations of JNJ-64281802.

5. STATISTICAL ANALYSES

5.1. General Considerations

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher. Figures can be generated in R.

Index cases participated for one visit only, therefore the next sections are only applicable to the HHCs. Descriptive statistics that will be provided for the index cases can be found in Appendix 3, Index Cases.

5.1.1. Analysis Phase Definition

The Prophylactic Dosing phase used for the safety evaluation and as defined below is extended compared to the Prophylactic Dosing phase as defined in the protocol considering the long half-life (~10 days) of the study intervention.

Following analysis phases are defined:

Table 1: Construction of analysis phases

Analysis phase	*Start date*	*End date*
Screening (phase 1)	The date & time of signing the informed consent*	1 minute before date & time of first study drug intake**.
Prophylactic Dosing (phase 2)	Date & time of first study drug intake** (JNJ - 64281802 or Placebo)	Minimum of: a. Date of Day 50 Visit at 23.59h*** b. Date of study termination at 23.59h
Follow-up (phase 3) ***	End of the Prophylactic Dosing phase +1 minute	Study termination date (date of last contact) at 23.59h

*: if no time is available then impute with 00:00
** If no time is available and randomization happened on the same day, then impute with randomization time.
*** If no Day 50 Visit was performed, the date of first study intervention intake + 49 days will be used. Participants recruited under protocol version 1 (dd. 09NOV2021) or earlier will not have a Follow-up phase and will have their prophylactic phase ending at Study termination date (date of last contact) at 23:59h.

5.1.2. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is the date of first study intervention intake. The relative day (reldy) of each visit will be defined as:

- reldy = visit date – reference date + 1 for visits on or after Day 1,
- reldy= visit date – reference date for visits before Day 1.

Consequently, there is no 'Day 0' defined.

If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point. Listed below (Table 2]) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 2: Visit Windows

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
[Antiviral Activity/ Immune]	[Screening]	[2]	[Baseline]	[<= 1]	[1]
	[Prophylactic]	[6]	[Day 5]	[1 to 7]	[5]
	[Prophylactic]	[10]	[Day 9]	[8 to 11]	[9]
	[Prophylactic]	[14]	[Day 13]	[12 to 15]	[13]
	[Prophylactic]	[18]	[Day 17]	[16 to 19]	[17]
	[Prophylactic]	[22]	[Day 21]	[20 to 23]	[21]
	[Prophylactic]	[26]	[Day 25]	[24 to 26]	[25]
	[Prophylactic]	[29]	[Day 28]	[27 to 34]	[28]
	[Prophylactic]	[30]	[Day 40]	[35 to 45]	[40]
	[Prophylactic]	[31]	[Day 50]	> 45	[50]
	[Follow-up]	[35]	[Day 90]	>45	[90]
[Clinical Laboratory]	[Screening]	[2]	[Baseline]	[<= 1]	[1]
	[Prophylactic]	-	[Unscheduled]	[1 to 11]	-
	[Prophylactic]	[14]	[Day 13]	[12 to 15]	[13]
	[Prophylactic]	-	[Unscheduled]	[16 to 26]	-
	[Prophylactic]	[29]	[Day 28]	[27 to 34]	[28]
	[Prophylactic]	-	[Unscheduled]	[35 to 45]	-
	[Prophylactic]	[31]	[Day 50]	> 45	[50]
[Vital Signs]	[Screening]	[1]	[Baseline]	[<= 1]	[1]
	[Prophylactic]	-	[Unscheduled]	[1 to 26]	-
	[Prophylactic]	[29]	[Day 28]	[27 to 34]	[28]
	[Prophylactic]		[Unscheduled]	[35 to 45]	
	[Prophylactic]	[31]	[Day 50]	> 45	[50]
[ECG]	[Screening]	[1]	[Baseline]**	[<= 1]	[1]
	[Prophylactic]	[4]/-	[Day 3]/[Unscheduled]#	[1,5]	[3]
	[Prophylactic]	-	[Unscheduled]	[6 to 15]	-
	[Prophylactic]	[29]	[Day 28]	[27 to 34]	[28]
	[Prophylactic]	-	[Unscheduled]	>34	-
[Physical examination]	[Screening]	[1]	[Baseline]	[<= 1]	[1]
	[Prophylactic]	-	[Unscheduled]	[1 to 44]	-
	[Prophylactic]	[31]	[Day 50]	> 45	[50]
[PK]	[Screening]	[1]	[Baseline]	[<= 1]	[1]
	[Prophylactic]	[4]	[Day 3]	[3]	[3]
	[Prophylactic]	[6]	[Day 5]	[4 to 6]	[5]
	[Prophylactic]	-	[Unscheduled]	[7]	-
	[Prophylactic]	[10]	[Day 9]	[8 to 10]	[9]
	[Prophylactic]	-	[Unscheduled]	[11]	-
	[Prophylactic]	[14]	[Day 13]	[12 to 14]	[13]
	[Prophylactic]	-	[Unscheduled]	[15 to 19]	-
	[Prophylactic]	[22]	[Day 21]	[20 to 22]	[21]
	[Prophylactic]	-	[Unscheduled]	[23 to 26]	-
	[Prophylactic]	[29]	[Day 28]	[27 to 29]	[28]
	[Prophylactic]	-	[Unscheduled]	[30 to 37]	-
	[Prophylactic]	[30]	[Day 40]	[38 to 42]	[40]
	[Prophylactic]	-	[Unscheduled]	[43 to 47]	-
	[Prophylactic]	[31]	[Day 50]	[48 to 52]	[50]
	[Prophylactic]	-	[Unscheduled]	[53 to 87]	-

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
	[Follow-up]	[35]	[Day 90]	[88,92]	[90]

* Relative to date of first study drug intake
** Up to 60 minutes after first study intervention intake
# PK substudy/other participants

5.2. Participant Dispositions

The number of HHCs in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants screened
- Participants randomized
- Participants who received study drug
- Participants who discontinued study drug
- Reasons for discontinuation of study drug
- Participants who completed the study
- Participants who terminated study prematurely
- Reasons for termination of study

This summary will be created separately for the safety, the primary, the secondary and the complete study population.

Listings of participants will be provided for the following categories:

- Participants who discontinued study drug
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study drug.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

All samples will be tested by a DENV RT-qPCR with a qualitative output. A sample is considered positive for DENV RNA in case the result is ‘target detected’.

In addition, all samples will be tested by the EUROIMMUN enzyme-linked immunosorbent assay (ELISA). The results of this test will be reported in relative units (RU)/ml and will be interpreted as follows:

– <8 RU/ml: negative
– ≥8 to <11 RU/ml: borderline

– ≥11 RU/ml: positive

A sample is considered DENV NS1 positive if the qualitative DENV NS1 result is positive (ie. quantitative DENV NS1 result ≥11 RU/ml). Samples are considered DENV NS1 negative for missing ELISA results and for borderline or negative qualitative ELISA results (ie. quantitative DENV NS1 result <11 RU/ml).

The primary endpoint is defined as presence or absence of a laboratory-confirmed DENV infection between baseline and the last day of dosing + 1 day. Presence of a 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 + 1 day will not be considered.

5.3.2. Level of Significance

The superiority of JNJ-64281802 above placebo will be tested at 20% one-sided significance level to assess PoC.

5.3.3. 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 , with a baseline 'target not detected (TND)' results for the DENV RT-qPCR assay and, if available, a negative/borderline NS1 protein assay result and with at least 1 post-baseline DENV RT-qPCR qualitative result up to and including the last day of dosing + 1 day.

Endpoint

Binary endpoint: presence or absence of a laboratory-confirmed DENV infection between baseline and last day of dosing + 1 day.

Interventions

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

Intercurrent Events

- Prohibited medication (when considered as major protocol deviation).
- Missed doses and dose interruptions: Missing a loading dose (LD), 2 consecutive maintenance doses (MDs), or 2 nonconsecutive MDs within a week.
- Overdose of study intervention (when considered as major protocol deviation).
- Wrong study intervention (when considered as major protocol deviation).

These intercurrent events will be handled using a "treatment policy strategy" (ie, data will be used as observed), with participants included in the study intervention group as randomized.

Population-level Summary

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

5.3.4. Analysis Methods

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 adjusted for stratification factor region. The odds-ratio from the logistic regression model will be used to estimate the PE. Given the expected low incidence, this is expected to be similar to the PE estimated using the relative risk. The calculated prophylactic efficacy (= 1 - odds ratio ≈ 1 - relative risk rate) will be used as the population-level summary. The superiority of JNJ-64281802 above placebo will be tested at 20% one-sided significance level as a PoC. The individual 1-sided CIs 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 region will be calculated together with the associated CIs.

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 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.

Subgroup Analyses

Subgroup analyses will be performed by geographic region (American Continent, Southeast Asia), country, serostatus at baseline (seronegative, defined as IgG <22 RU/mL, seropositive defined as IgG ≥22 RU/mL) and age (<40 years, >=40 years) upon the condition that at least 6 cases are observed in the subgroup and over the combined placebo and active study intervention group for which the comparison is done.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Secondary Endpoint(s)

5.4.1.1. Definition of Endpoint(s)

The key secondary endpoint is defined as presence or absence of laboratory-confirmed symptomatic DENV infection between baseline and last day of dosing + 1 day. Laboratory-confirmed symptomatic DENV infection is defined as having at least 2 solicited systemic AEs, of which at least one is a most common dengue symptom (see Table 3), lasting for ≥1 day and

occurring within a +/-2 days time window around the positive PCR or NS1 test. If a sample is missing and the next or prior available sample is positive for a DENV infection, the missing sample will be considered as positive for DENV infection as well. Consequently, solicited AEs observed within +/-2 days around the scheduled missing sample date will be considered as well as a confirmation of a symptomatic DENV infection.

Table 3: Solicited systemic AEs

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

* Most common dengue symptom

5.4.1.2. Level of Significance

If a significant reduction in the number of laboratory-confirmed DENV infections in the primary study population is established for the HDR, the superiority of JNJ-64281802 above placebo will be tested in the FA at 20% one-sided significance level.

5.4.1.3. Estimand

The key secondary 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 fulfil with one of the following conditions:

- no evidence of current DENV infection at baseline (based on target not detected (TND) results for DENV RNA assay and, if available, a negative/borderline result for NS1 protein assays) and with at least 1 result for DENV RNA or NS1 protein assay available post baseline up to and including the last day of dosing + 1 day (ie. the primary study population),

  or

- asymptomatic for dengue at screening, but with evidence of current DENV infection (based on positive results for DENV RNA or NS1 protein assays at baseline) (ie. the secondary study population).

Endpoint

Binary endpoint: presence or absence of a laboratory-confirmed symptomatic DENV infection between baseline and last day of dosing + 1 day.

Interventions

Depending on the result of the primary analysis:

- If a significant reduction in laboratory-confirmed DENV infections is established for the LDR in the primary study population: Participants on a high- or low-dose JNJ-64281802 regimen (combined), or matching placebo in a double-dummy fashion under fed conditions.
- If no significant reduction in laboratory-confirmed DENV infections is established for the LDR in the primary study population: Participants on a high-dose JNJ-64281802 regimen, or matching placebo in a double-dummy fashion under fed conditions.

Intercurrent Events

- Prohibited medication (when considered as major protocol deviation).
- Missed doses and dose interruptions: Missing a LD, 2 consecutive MDs, or 2 nonconsecutive MDs within a week.
- Overdose of study intervention.
- Wrong study intervention (when considered as major protocol deviation)

These intercurrent events will be handled using a "treatment policy strategy" (ie, data will be used as observed), with participants included in the study intervention group as randomized.

Population-level Summary

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

5.4.1.4. Analysis Methods

The key secondary hypothesis in this study is that JNJ-64281802 is superior to placebo with respect to prevention of laboratory-confirmed symptomatic DENV infection between baseline and last day of dosing + 1 day in the complete study population.

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 on the primary endpoint (as described in Section 5.3).
2. Comparing the number of events of the HDR with the placebo regimen, if only the HDR showed a significant effect on the primary endpoint.

Laboratory-confirmed symptomatic DENV infections will be analyzed similarly as the primary endpoint with the model adjusted for both the stratification factor (region) and DENV infection at baseline (primary/secondary study population). This includes the subgroup analyses as described in section 5.3.4.

5.4.2. Supportive Secondary Analysis

5.4.2.1. Symptomatic DENV infections

Supportive analysis will be done with the objective to evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection between baseline and last day of dosing + 1 day among HHC who have no evidence of current DENV infection at baseline (ie. the primary study population).

The same definition, significance level, attributes and analysis methods as for the key secondary endpoint will be used (see 5.4.1), with exception of the population attribute as the population is restricted to the primary study population.

No subgroup analyses will be done for this endpoint.

5.5. Exploratory Endpoint(s) Analysis

5.5.1.1. DENV infections

For IgG antibodies the actual values (RU/mL) will be available. Collected unquantifiable data of apassessments on anti DENV IgG Immunology will be handled according to the rules summarized in Table 4.

Table 4: Data Handling Rules for anti DENV IgG Immunology Assessments

DENV Parameter	Quantitative Limits			
	LOD/ LLOQ	ULOQ	Imputed Values	
			TND/ <LLOQ, TD [1]	>ULOQ[2]
IgG antibodies (RU/mL) [4]	2 (LLOQ)	280	1 (<LLOQ, TD)	308

[1] LOD/2 or LLOQ/2
[2] ULOQ+(ULOQ/10)

Exploratory analysis will be done to evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection among HHC who have no evidence of current DENV infection at baseline (ie. the primary study population) using different definitions of DENV infection:

- through increase of 1.5 in anti-DENV antibody between baseline and Day 40 ,
- through increase of 1.5 in anti-DENV antibody between baseline and Day 50,
- through increase of 1.5 in anti-DENV antibody between baseline and Day 90,

on condition that the increase results in a value > 22 RU/mL (=cut-off level).

The cut-off for the increase in anti-DENV antibody might be updated during the analysis.

The same significance level, attributes and analysis methods as for the primary endpoint will be used (see 5.4.1).

No subgroup analyses will be done for this endpoint.

5.5.1.2. Analyses by Serotype

Analyses by serotype to evaluate the prophylactic efficacy against DENV infection and against symptomatic DENV infection will be done upon the condition that at least 6 cases of the same serotype are observed over the JNJ-64281802 and placebo in group that will be compared.

In this analysis, a laboratory confirmed DENV infection is defined through the detection of DENV RNA of a specific serotype between baseline and the last day of dosing + 1 day. Infections with other serotypes will be excluded from this analysis.

The same significance level, attributes and analysis methods as for the primary and key secondary endpoint will be used (see sections 5.3 and 5.4.1).

No sensitivity or subgroup analyses will be done for these analyses.

5.5.1.3. Quantitative DENV RNA VL Levels

Descriptive analyses will be done to evaluate

- the prophylactic effect of JNJ-64281802 with respect to reduction of DENV RNA among enrolled HHC who have no evidence of current DENV infection at baseline and who are infected post baseline
- the antiviral effect of JNJ 64281802 as early treatment among HHC who have evidence of DENV infection at baseline.

Data Handling Rules

Serum DENV RT-qPCR levels will be assessed using a validated quantitative DENV RT - qPCR assay.

Measurements collected from screening visit to the end of study below the lower limit of detection (LOD) and below/above the lower/upper limit of quantification (LLOQ/ULOQ) for each of the 4 serotypes on this assay will be handled according to the rules summarized in Table 5.

Table 5: Data Handling Rules for DENV RT-qPCR levels (copies/mL)

Serotype	LOD	LLOQ	ULOQ	Imputed Values		
				target not detected[1]	<LLOQ target detected[2]	>ULOQ[3]
DENV-1	29	1000	1 000 000 000	15	500	1 100 000 000
DENV-2	60	1000	1 000 000 000	15	500	1 100 000 000
DENV-3	36	1000	1 000 000 000	15	500	1 100 000 000
DENV-4	55	1000	1 000 000 000	15	500	1 100 000 000

(1) LOD (from DENV-1)/2 rounded to the nearest integer
(2) LLOQ/2
(3) ULOQ+(ULOQ/10)

Before any other rule is applied, the value for each day is defined as the maximum value of assessments performed on that day for each assay (DENV-1, DENV-2, DENV-3 and DENV-4). This is applied for each day separately.

Endpoint Definitions

Measurement	Formula/Definition
Reduction of DENV RNA among HHC who have no evidence of current DENV infection at baseline and who are infected post baseline	
Peak of detectable DENV RNA	Maximum of all measured DENV RNA values
Antiviral effect of JNJ 64281802 as early treatment among HHC who have evidence of current DENV infection at baseline	
Peak of post baseline detectable DENV RNA	Maximum of all post-baseline measured DENV RNA values
Time to end of detectable DENV RNA	Minimum of (days with undetectable DENV RNA after the last detectable DENV RNA result) – Day 1 + 1 If the last measured DENV RNA result is still detectable, the value will be censored at the last available sample.

Analysis Methods

Reduction of DENV RNA among HHC who have no evidence of current DENV infection at baseline and who are infected post baseline:

Descriptive statistics on peak of detectable DENV RNA will be calculated for each study intervention group separately. Statistics include sample size (n), mean, SD, median, minimum, and maximum.

Antiviral effect as early treatment among HHC who have evidence of current DENV infection at baseline:

Descriptive statistics on peak of post-baseline detectable DENV RNA will be calculated for each study intervention group separately. Statistics include sample size (n), mean, SD, median, minimum, and maximum.

Time-to end of detectable DENV RNA will be analyzed using Kaplan-Meier (KM) estimates. A summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles, and median time-to-event, with 95% CIs based on log-log transformation method, will be presented. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by study drug.

5.5.1.4. DENV-associated signs and symptoms

To evaluate the antiviral effect of JNJ-64281802 as early treatment among HHC who have evidence of DENV infection at baseline, descriptive analyses will be done on the DENV-associated signs and symptoms.

DENV-associated signs and symptoms are defined as the reported solicited adverse events (Table 3). Tabulations will be provided showing the proportion of subjects per reported adverse events.

Time to end of end of DENV Infection-associated AEs will be defined as the time between the minimum of all start dates and the maximum of all end dates+1 day and will be censored if there are still signs & symptoms present at Day 28. Time to end of end of DENV Infection-associated AEs will be analyzed using Kaplan-Meier (KM) estimates. A summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles, and median time-to-event, with 95% CIs based on log-log transformation method, will be presented. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by study drug.

5.5.1.5. DENV Infections in Follow-up

Individual data on DENV Infections observed in follow-up period will be provided.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set and actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include: N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who received study intervention will be summarized by study intervention group.

Study intervention duration is defined as:

> date of last dose of study intervention – date of first dose of study intervention +1 (including days off study intervention).

Duration of intervention will be summarized in the following duration categories:

> [<1 week, 1-<2 weeks, 2-<3 weeks, 3-<4 weeks, 4 weeks].

Total dosing days of intervention is defined as:

> total number of days that study intervention was taken by the participant (excluding days off study intervention).

Compliance is defined as:

> Compliance (%) = 100 x Total dosing days of intervention/Study intervention duration

Study intervention compliance will be summarized descriptively. In addition, compliance will be summarized in the following categories:

- The number of full compliant participants,
- The number of participants for which >= 1 LD was missed,
- The number of participants for which >= 1 MD was missed,
- The number of participants with 2 consecutive missed MDs,
- The number of participants with > 1 missed MDs within a week.

Exposure and compliance will be given for each of the following population: safety, primary, secondary and complete study population.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to report adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0). Any AE occurring at or after the initial administration of study intervention 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 will be considered as treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent (TE), unless the AE is reported based on a baseline laboratory result, in which case the AE will be assigned to the screening phase. The list of coded AE terms that are based on a laboratory result is included in appendix 8 (section 6.8). If the event date is recorded as partial or completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Separate tables and participants listings will be created for solicited (see Table 3) and unsolicited adverse events, showing the results by study intervention group.

Summary tables by study intervention group will be provided for adverse events by phase (Prophylactic Dosing, Follow-up and both phases combined):

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study intervention/termination of study participation
- AEs by toxicity grade assigned by the investigator, based upon protocol appendix 9.
- AEs by relationship to study intervention
- AEs leading to dose interruption of study intervention

In addition to the summary tables, participants listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation/interruption of study intervention or termination of study participation

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments (if applicable)

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set and will be restricted to the laboratory tests as required by Section 10.8 appendix 8 of the protocol, with exception of the differential WBC counts for which the level of data cleaning was deemed insufficient (neutrophils, lymphocytes, monocytes, eosinophils and basophils). The analysis of laboratory data will be done at the level of standardized values and units.

As for some laboratory tests local labs are used for the value determination, pooled results over the different labs will only be provided on the categorical results, ie. based on the normal limits or

based on toxicity grades. The laboratory reference ranges from the lab where the samples were analyzed will be used to determine the laboratory abnormalities or toxicity grades.

Toxicity grades will be determined according to the Table for Laboratory Abnormalities as shown in the original protocol (dated 09 November 2021), or, if not available, as shown in protocol amendment 3 (dated 19 July 2023), Section 10.9 Appendix 9 and will be attributed to the baseline and postbaseline values. In case no toxicity grades are defined for a test, the abnormalities (below/above normal ranges) will be used.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For toxicity grades, treatment emergence (TE) will be concluded if the postbaseline grade is worse than the baseline grade.
- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.
- The worst TE grade/abnormality will be determined. The worst TE toxicity grade is the highest grade reached. For non-graded abnormalities, the 'low' and 'high' classes are equally worse, both will be considered as worst abnormality.

A summary table will show the number and percentage of participants per TE abnormality. Shift summaries from baseline laboratory value to the worst toxicity grade/abnormality in chemistry and hematology tests will be presented by intervention group.

Descriptive statistics and mean ± SE graphs by lab and by study intervention will be presented at scheduled time points on actual values and changes from baseline for chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests restricted to the laboratory tests for the labs in which at least 100 participants were analyzed.

In addition to the above tables, summary listings will be provided for all participants with treatment-emergent abnormal laboratory values of at least grade 2, or with reported clinically significant laboratory results whether treatment-emergent or not. This listing will include all other time points for the corresponding participant/parameter.

5.6.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including pulse and blood pressure (systolic and diastolic) will be summarized at each scheduled assessment time point. Change from baseline will be summarized by intervention group. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

According to protocol, vital signs parameters should have been collected in supine position. However, if these are not available, available standing or semi-recumbent position can be used.

Abnormality grades will be determined according to 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 where values were absent (see Table 6) and will be attributed to the baseline and postbaseline values.

Table 6: Graded Abnormal Vital Signs

Vital Sign	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pulse (bpm)			
Tachycardia	>100-115	>115-130	>130
Bradycardia	50-54	<50-45	<45
Systolic blood pressure (mmHg)			
Hypertension (Systolic)	141-150	>150-155	>155
Hypotension (Systolic)	85-89	80-<85	<80
Diastolic blood pressure (mmHg)			
Hypertension (Diastolic)	91-95	>95-100	>100

Postbaseline values will be compared with their corresponding baseline values.

- TE will be concluded if the postbaseline grade is worse than the baseline grade.
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.
- The worst TE grade will be determined. The worst TE toxicity grade is the highest grade reached.

A summary table will show the number and percentage of participants per emergent abnormality. In addition, shift summaries from baseline value to the abnormality will be presented by intervention group.

A listing of abnormal individual participant vital signs values from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding participant/parameter

All abnormal physical examination results will be listed, including clinical significance specifications if/as provided.

5.6.3.3. Electrocardiogram

The ECG parameters as measured by the central monitoring that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB) and Fridericia's formula (QTcF)[3,4].

QTcB and QTcF values will be used as reported by central ECG lab, they will not be recalculated.

If ECG measurements are repeated at a visit, only the first measurement will be considered in the 'Visit' ECG result. The repeat measurements can be used for the worst TE grade/abnormality as explained below.

Descriptive statistics (mean, standard deviation, median and ranges) of actual ECG parameters and change from baseline will be summarized by intervention group at each scheduled time point.

The actual values for HR, PR, QRS, QTcB and QTcF and the changes from baseline for QTcB and QTcF will be categorized into abnormalities using the boundaries defined in Table 7.

Table 7: Criteria for Abnormal QTc Values and Changes from Baseline

Abnormality class and label	ECG parameter			
	HR (bpm)	**PR (ms)**	**QRS (ms)**	**QTcB and QTcF**
Abnormalities for actual values				
Low	< 45	< 110	-	-
High	≥ 120	≥ 220	≥ 120	-
]450, 480] ms M/F (*)				> 450 - ≤ 480
]450, 480] ms M/F (*)				> 470 - ≤ 480
]480, 500] ms				> 480 - ≤ 500
> 500 ms				> 500
Abnormalities for change from baseline				
]30, 60] ms				> 30 - ≤ 60
> 60 ms				> 60

(*) The boundaries for QTcB and QTcF abnormalities are different for males and females, but the same abnormality label will be used.

No abnormalities will be defined for uncorrected QT, but uncorrected actual QT values >500 ms will be flagged and only shown in listings. Actual QTc values ≤450 ms are considered as normal, as well as all changes ≤30 ms.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.
- When changes from baseline are concerned (QTcB/QTcF), abnormality classes are always TE, per definition.
- The worst TE grade/abnormality by phase will be determined. For non-graded abnormalities, the ‘low’ and ‘high’ classes are equally worse, both will be considered as worst abnormality.

A summary table will show the number and percentage of participants per emergent abnormality for the prophylactic phase. A cross-tabulation of the worst abnormality versus baseline will be presented by intervention group.

A tabulation of the worst QT/QTc change versus baseline will be presented by study intervention.

A listing of clinically relevant ECG abnormalities from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding participant/parameter.

Subgroup Analyses

Subgroup analysis for the participants included PK substudy will be performed.

5.7. Other Analyses

5.7.1. Pharmacokinetics

All HHCs who received at least 1 dose of study drug and have at least 1 plasma concentration value after administration will be included in the analysis. Individual JNJ-64281802 plasma concentrations will be listed and summarized with descriptive statistics (n, mean, SD, geometric mean, median, minimum, maximum and interquartile ranges) by dose. Individual and summarized plasma concentration results may be graphically presented by dose and at selected time points. In this graphical presentation, special attention will be given to plasma concentration profiles of HHCs who have a lab-confirmed DENV infection between baseline and the last day of dosing + 1 day. Special attention to plasma concentration-time profiles may also be given to individuals with SAEs.

5.7.2. Viral Genome Sequencing

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.

The list of positions of interest might be updated during the analysis.

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 analysed.

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 subgroups and intervention groups.

A separate SAP and virology report may be prepared.

5.7.3. Biomarkers

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 are not part of this SAP. The analyses will always be under the supervision of the sponsor.

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

5.7.4. Data Monitoring Committee (DMC) or Other Review Board

An IDMC was commissioned for this study and reviewed unblinded safety data on a regular basis throughout the conduct of this study to ensure participant safety. The committee did meet periodically to review these safety data.

At any point during the study, following any reviews of safety, PK and/or IAs data, the IDMC had the authority to recommend to the Sponsor Committee modifications to the study conduct and/or to the safety assessments, or to halt a dose arm due to safety concerns. Based on the recommendations of the IDMC, the Sponsor Committee could decide that changes to the study should be implemented.

Further details on the composition of the IDMC, the content of the data package and the frequency of the meetings are available in the IDMC charter.

The regular IDMC analyses followed this SAP, but data was restricted to the following:

Index Case Data	
Index cases	section 6.3
General Information Data	
Participant Dispositions	section 5.2
Demographics and Baseline Characteristics	section 6.4
Protocol Deviations	section 6.5
Extent of Exposure	section 5.6.1
Efficacy Data	
Primary Endpoint(s) Analysis	section 5.3
Safety Data	
Adverse Events	section 5.6.2
Clinical Laboratory Tests	section 5.6.3.1
Vital Signs and Physical Examination	section 5.6.3.2
Electrocardiogram	section 5.6.3.3
Other Analyses Data	
Pharmacokinetics	section 5.7.1

A Separate DPS specifying the outputs created for the IDMC analyses is also produced.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ATC	anatomic and therapeutic class
AUC	area under the curve
AUC_{τ}	area under the concentration curve during one dosing interval
BMI	body mass index
CI	confidence interval
Cmax	maximum concentration
CPAP	Clinical pharmacology analysis plan
CRF	Case report form
C_{trough}	observed analyte concentration just prior to the beginning or at the end of a dosing interval
DENV	Dengue virus
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
FA	Final analysis
FDA	Food and Drug Administration
HDR	High dose regimen
HHC	Household contact
IA	Interim Analysis
ICF	Informed consent form
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IWRS	interactive web response system
LD	Loading dose
LDR	Low dose regimen
LLOD	lower limit of detection
LLOQ	Lower limit of quantification
MD	Maintenance dose
MedDRA	Medical Dictionary for Regulatory Activities
MSR	Modelling and simulation report
NAb	neutralizing antibodies
NS	Non-structural protein
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PE	Prophylactic efficacy
PK	pharmacokinetic(s)
PoC	Proof-of-concept
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid
RT	Reverse transcription
SAE	serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis sofware
SD	standard deviation
SE	Standard error
SMQs	standardised MedDRA queries
SSG	Statistical support group
Tmax	time to maximum concentration
VL	Viral Load
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

1) Minor updates and clarifications are made to the primary estimand when compared to the definition in the protocol. The modifications are done based on the available data and new insights on the detectability of a laboratory confirmed DENV infection using different assays:

   - 1 extra day is added to the observation period of the endpoint because for some participants the Day 28 assessment is performed 1 day after the last dose,

   - intercurrent events are modified and clarified: fasted intake of study intervention is not considered as intercurrent event based on the quality of the data collected for this purpose, clarifications are added to the missed doses and treatment interruptions, overdose of study intervention and wrong IP have been added as intercurrent events.

   - the stratification factor 'country' is updated to 'region' in the logistic model used for the primary estimand of the prophylactic efficacy to avoid quasi-complete separation of data points due to the low number of events. Similarly, region is used as the stratification factor in the Mantel-Haenszel stratum-weighted estimator of the risk difference.

   - the 2-sided confidence interval was updated to a corresponding 1-sided confidence interval.

2) The definition of the complete study population is updated to "All participants included in the primary or secondary study population": a minimum of DENV RNA and/or NS1 protein assay data should be available to be able to confirm by laboratory data that the signs and symptoms are caused by a DENV infection.

3) The study was prematurely ended on 02 October 2024 when 21 laboratory confirmed dengue infections between baseline and last day of dosing (+1 day) were observed in the primary analysis population and 14 symptomatic dengue infection between baseline and last day of dosing (+1 day) were observed in the complete study population. This decision was taken by Johnson & Johnson based on portfolio reprioritization and was not based on any safety concerns.

   Because of this early termination, the following changes to the per protocol-planned analyses are done: the planned IA is skipped, the sensitivity estimators for the primary objective are not calculated, the PK analyses is restricted to descriptive statistics on the individual plasma concentration-time data, the PK/PD analyses are not done, some exploratory analyses are left out and the analysis is considered final.

The following exploratory analysis are left out:

- Exploratory analysis on the prophylactic effect of JNJ-64281802 with respect to the prevention of DENV infection as measured by DENV ribonucleic acid (RNA)

- Exploratory analysis on the prophylactic effect of JNJ-64281802 as measured through detection of DENV NS1 protein

It is clear from the available data that all laboratory confirmed DENV infections have detectable RNA on at least 1 time point, while only a minority have detectable DENV NS1 protein.

- Exploratory analysis to evaluate the prophylactic effect of JNJ-64281802 with respect to the prevention of symptomatic DENV infection up to Day 40, Day 50 and Day 90

Only isolated cases of symptomatic DENV infections after the last dose of study intervention are observed.

6.3. Appendix 3 Index Cases

Index cases will participate for one visit only.

Disposition

The number of Index cases in the following disposition categories will be summarized:

- Index cases enrolled
- Index cases for which the DENV infection was confirmed by the central lab test

An overview will be provided by region, country and site ID, showing per index case the number of HHCs (1, 2, 3 or > 3) that entered in the trial.

A summary will be provided of the different serotypes per region/country and clinical site.

Viral sequencing.

Exploratory analysis will be done to determine the circulating DENV serotypes/genotypes among the index cases.

6.4. Appendix 4 Demographics and Baseline Characteristics of the HHCs

The number of participants in each analysis set will be summarized and listed by intervention group and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

Table 8 presents a list of the demographic variables that will be summarized by intervention group and overall for the primary, secondary and safety analysis set.

Table 8: Demographic Variables

Continuous Variables:	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age ([≤25 years, 26-40 years, 41-55 years, and > 55 years])	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m2, normal 18.5-<25 kg/m2, overweight 25-<30 kg/m2, obese >=30 kg/m2])	
Region ((Asia-Oceania (APAC), Europe and Middle East and Africa (EMEA), North America (NA), and Latin America and the Caribbean (LATAM))	
Country	
Baseline Serology (IgG) (<16 relative units (RU)/mL (negative); ≥16 to <22 RU/mL (borderline); ≥22 RU/mL (positive))	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.5. Appendix 5 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Missed doses
- Other

6.6. Appendix 6 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continued after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC1 and ATC2 term, standardized medication name, intervention group, and study phase (prophylactic, follow-up and combination of prophylactic and follow-up). The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior medications will be listed.

6.7. Appendix 7 Medical History

The medical history will be listed.

6.8. Appendix 8 Laboratory Related Adverse Events Coded Terms

The following adverse events are related to laboratory assessments and will be assigned to the screening phase when the start date equals the date of first study drug intake:

AEBODSYS	AEDECOD
Blood and lymphatic system disorders	Anaemia
Blood and lymphatic system disorders	Eosinophilia
Blood and lymphatic system disorders	Hypochromic anaemia
Blood and lymphatic system disorders	Iron deficiency anaemia
Blood and lymphatic system disorders	Leukocytosis
Blood and lymphatic system disorders	Lymphadenopathy
Blood and lymphatic system disorders	Microcytic anaemia
Blood and lymphatic system disorders	Neutropenia
Blood and lymphatic system disorders	Normochromic normocytic anaemia
Blood and lymphatic system disorders	Normocytic anaemia
Blood and lymphatic system disorders	Thrombocytopenia
Blood and lymphatic system disorders	Thrombocytosis
Hepatobiliary disorders	Hyperbilirubinaemia
Infections and infestations	Asymptomatic bacteriuria
Infections and infestations	Pyuria
Investigations	Activated partial thromboplastin time prolonged
Investigations	Alanine aminotransferase decreased
Investigations	Alanine aminotransferase increased
Investigations	Amylase increased
Investigations	Aspartate aminotransferase decreased
Investigations	Aspartate aminotransferase increased
Investigations	Bacterial test
Investigations	Blood alkaline phosphatase
Investigations	Blood alkaline phosphatase increased
Investigations	Blood bilirubin increased
Investigations	Blood cholesterol increased
Investigations	Blood creatine phosphokinase
Investigations	Blood creatine phosphokinase increased
Investigations	Blood glucose decreased
Investigations	Blood glucose increased
Investigations	Blood lactate dehydrogenase increased
Investigations	Blood phosphorus decreased
Investigations	Blood potassium increased
Investigations	Blood pressure increased
Investigations	Blood triglycerides increased
Investigations	Blood uric acid increased
Investigations	Blood urine present

Investigations	Gamma-glutamyltransferase increased
Investigations	Glucose urine present
Investigations	HIV test positive
Investigations	Haemoglobin decreased
Investigations	Hepatic enzyme increased
Investigations	Lipase increased
Investigations	Low density lipoprotein increased
Investigations	Lymphocyte count decreased
Investigations	Nitrite urine present
Investigations	Platelet count decreased
Investigations	Protein urine
Investigations	Protein urine present
Investigations	Prothrombin time prolonged
Investigations	Red blood cell sedimentation rate
Investigations	Red blood cell sedimentation rate increased
Investigations	Red blood cells urine
Investigations	Red blood cells urine positive
Investigations	Transaminases increased
Investigations	Urine ketone body present
Investigations	White blood cell count
Investigations	White blood cell count increased
Investigations	White blood cells urine
Investigations	White blood cells urine positive
Metabolism and nutrition disorders	Diabetes mellitus
Metabolism and nutrition disorders	Dyslipidaemia
Metabolism and nutrition disorders	Hyperamylasaemia
Metabolism and nutrition disorders	Hypercalcaemia
Metabolism and nutrition disorders	Hypercholesterolaemia
Metabolism and nutrition disorders	Hyperglycaemia
Metabolism and nutrition disorders	Hyperkalaemia
Metabolism and nutrition disorders	Hyperphagia
Metabolism and nutrition disorders	Hypertriglyceridaemia
Metabolism and nutrition disorders	Hyperuricaemia
Metabolism and nutrition disorders	Hypoalbuminaemia
Metabolism and nutrition disorders	Hypocalcaemia
Metabolism and nutrition disorders	Hypoglycaemia
Metabolism and nutrition disorders	Hypokalaemia
Metabolism and nutrition disorders	Hyponatraemia
Metabolism and nutrition disorders	Hypophosphataemia
Metabolism and nutrition disorders	Hypoproteinaemia
Metabolism and nutrition disorders	Impaired fasting glucose
Metabolism and nutrition disorders	Type 2 diabetes mellitus

Renal and urinary disorders	Glycosuria
Renal and urinary disorders	Haematuria
Renal and urinary disorders	Leukocyturia
Renal and urinary disorders	Proteinuria

7. REFERENCES

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