Janssen Research & Development

Statistical Analysis Plan

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

Protocol 64281802DNG2003; Phase 2

JNJ-64281802

Status:	Final
Date:	04 OCT 2023
Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.:	EDMS RIM-298496

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 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	04 October 2023	Not Applicable	Initial release

1. INTRODUCTION

On 14-Sep-2023, the Sponsor decided to terminate study 64281802DNG2003 early due to low enrollment and not for any safety-related reasons. Five participants were enrolled into the study. The last enrollment was on 19-Sep-2022. Although a stable draft version of the Statistical Analysis Plan (SAP) of the study was ready (available in RIMdocs EDMS-RIM-298496 V0.4), it was decided to simplify and reduce the statistical outputs to listings and individual patient profiles because data of only five randomized participants were collected. Therefore, no summary statistics across participants will be produced, and data will be reported as a listing generated for each participant (patient profile) and clinical narratives. In addition, graphical representations will be created for selected virological parameters.

This SAP contains identification of variables that will be included in the patient profiles, a description of graphs for virological parameters, and definitions of derived variables. This SAP describes the analysis for the clinical study report (CSR). The SAP is to be interpreted in conjunction with the protocol.

Due to the small number of participants no pharmacokinetic (PK) or pharmacokinetic/ pharmacodynamics (PK/PD) analysis will be performed, and only observed plasma levels of JNJ-64281802 will be reported in the CSR.

1.1. Objectives and Endpoints

Given the small number of enrolled participants, no formal analyses will be performed to evaluate the study objectives listed below (list from Protocol amendment 6 dated 06-June-2022). Only individual patient profiles and graphs for selected virological parameters will be provided.

Primary Objective

The primary objective of this study is to investigate the antiviral activity of JNJ-64281802 versus placebo in terms of a reduction in DENV RNA in primary DENV infection and as measured by the area under the $\log_{10}$-transformed DENV - 1 RNA viral load concentration-time curves from baseline until Day 5 ($AUC_{D1\text{-}D5}$ [VL]).

Secondary Objectives

Objectives	Endpoints
Secondary	
• Assess the safety and tolerability of JNJ-64281802 in primary and secondary DENV infection	• AEs • ECGs • physical examinations • vital signs • clinical laboratory assessments
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on other	• Virologic endpoints derived from the DENV RNA, including

Objectives	Endpoints
virological endpoints in primary DENV infection	– Occurrence of detectable DENV RNA at each time point in primary DENV infection – Time to undetectable DENV RNA in primary DENV infection
• Evaluate the PK of JNJ-64281802	• PK parameters for JNJ-64281802
Exploratory	
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on DENV infectious viral titer (further referred to as viremia) in primary DENV infection	• Virologic endpoints derived from viremia, including – Area under the log_{10}-transformed viremia curve from baseline until Day 5 in primary DENV infection – Occurrence of detectable viremia at each timepoint in primary DENV infection – Time to undetectable viremia in primary DENV infection
• To explore the relationship between the exposure and antiviral activity of JNJ-64281802	• PK (plasma concentrations or exposure parameters) of JNJ-64281802. • Area under the log_{10}-transformed viremia or DENV RNA viral load.
• Investigate the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV RNA in secondary DENV infections and in all DENV infections	• Virologic endpoints derived from the DENV RNA, viral load, including – Area under the log_{10}-transformed DENV RNA viral load curve from baseline until Day 5, in secondary DENV infection – Occurrence of detectable DENV RNA at each time point in secondary DENV infection – Time to undetectable DENV RNA in secondary DENV infection
• Investigate the antiviral activity of JNJ-64281802 versus placebo based on viremia in secondary DENV infections and in all DENV infections	• Virologic endpoints derived from viremia, including – Area under the log_{10}-transformed viremia curve from baseline until Day 5 in secondary DENV infection – Occurrence of detectable viremia at each timepoint in secondary DENV infection – Time to undetectable viremia in secondary DENV infection
• Investigate the effect of JNJ-64281802 versus placebo on the change in hematology values over time (leucocytes, platelets, and hematocrit)	• The maximal decrease from baseline (per participant) observed in platelet counts from Day 2 to Day 5 • The maximal decrease from baseline (per participant) observed in leucocyte counts from Day 2 to Day 5 • The maximal increase from baseline (per participant) observed in hematocrit concentration from Day 2 to Day 5
• Investigate the effect of JNJ-64281802 versus placebo on the immunological profile	• The occurrence and magnitude of anti-DENV total IgM and IgG antibody titers

Objectives	Endpoints
• To explore the effect of JNJ-64281802 versus placebo on DENV-related clinical signs and symptoms	• Time to resolution of dengue signs and symptoms • Severity of dengue signs and symptoms
• To assess changes in the viral genome sequence (with a focus on NS4B) in participants with detectable DENV RNA	• Changes in the viral genome sequence at and between first viral isolation and last viral isolation
• To explore the DENV NS1 serum protein levels	• Occurrence and magnitude of DENV NS1 serum protein levels
• To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802	• HLA genotyping and pharmacogenomic analyses
The following additional exploratory objectives may be evaluated at the discretion of the sponsor: • Investigate the effect of JNJ-64281802 versus placebo on immunological profile based on occurrence and magnitude of anti-DENV cellular immune responses • To explore changes in serum protein levels (including cytokines) • To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802 based on biomarker analysis via transcriptional profiling of host RNA • The occurrence and magnitude of an anti-DENV neutralizing antibody response	

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

1.2. Study Design

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

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

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

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

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

2. STATISTICAL HYPOTHESES

The primary hypothesis of this study is that JNJ-64281802 is superior to placebo with respect to reduction in viral load in participants with a primary DENV infection, as measured by area under the $\log_{10}$-transformed DENV RNA viral load curve from baseline on Day 1 until Day 5.

3. SAMPLE SIZE DETERMINATION

The study planned to recruit in total 150 participants, with the primary objective of investigating the antiviral activity of JNJ-64281802 versus placebo based on DENV RNA in primary DENV infection and with a secondary objective to describe the safety and tolerability of JNJ-64281802 in participants with DENV infection.

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

To assess sample size requirements for this hypothesis, data of 47 DENV RNA curves were estimated similar to the DENV RNA curves graphically presented in the balapiravir trial. All curves were considered as balapiravir did not have an effect on the viral load. A limit of detection of 2.3 log copies/mL was assumed. Although the majority of the population included in the balapiravir trial suffered from a secondary infection[2], these estimated DENV RNA curves were considered representative for a primary infected dengue population. As the clearance of DENV RNA occurs earlier and faster in patients with secondary dengue, this is a conservative assumption[3].

The 47 estimated DENV RNA curves were used to calculate the means, standard deviations and correlations of the $\log_{10}$ viral loads over time. These calculated values were thereafter used to

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

The specificity of the DENV NS1 testing at baseline is estimated to be 98% which entails that 2% of participants that will be enrolled will not be evaluable for efficacy. Based on literature[1], it is estimated that approximately 60% of the total population will have a primary infection. Furthermore, it is anticipated that approximately 4% of the enrolled participants drop-out for other reasons. The study will therefore need to recruit a total of 150 participants in order to achieve a sample of 84 participants to achieve >80% power on the primary hypothesis.

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

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Patient profiles will be produced for all participants who signed the ICF and who were randomized and treated in the study.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Analysis Phase Definition

No analysis phases will be derived.

5.1.2. Visit Windows

All values collected for the parameters listed below will be considered based on their actual date and time.

5.1.3. Baseline Definition

Not applicable.

5.1.4. Relative Day

Study Day 1 is defined as the date of first study intervention intake (reference day). All complete dates reported in the patient profiles will be assigned a day relative to this date.

The relative day (reldy) 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.

5.1.5. Definition of Subgroups

Not applicable.

5.1.6. Demographics and Baseline Characteristics

Table 2 presents the list of demographic variables that will be reported in the patient profiles.

Table 2 – Demographic variables

Variables listed in patient profile
Age (years)
Weight at baseline (kg)
Height at baseline (cm)
BMI (kg/m^2)
Sex [Female; Male; Unknown; Undifferentiated]
Race[a] [American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or other Pacific Islander; White; Multiple; Not reported; Unknown]
Ethnicity [Hispanic or Latino; Not Hispanic or Latino; Not reported; Unknown]
Country

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

Table 3 presents the list of baseline characteristics that will be reported in the patient profiles.

Table 3 – Baseline Characteristics

Variables listed in patient profile
Dengue NS1 rapid test result at screening/baseline [Positive; Negative; Equivocal]
Anti-Dengue IgG rapid test result at screening/baseline [Positive; Negative; Equivocal]
Anti-Dengue IgM rapid test result at screening/baseline [Positive; Negative; Equivocal]
Dengue RT-PCR test results at screening/baseline [Positive; Negative]
Duration of onset of fever until time of randomization (hours) [date/time of randomization – date/time of fever onset]
Does the subject have dengue hemorrhagic fever (DHF) at screening/baseline? [Yes; No] If yes, list symptoms
Does the subject have dengue shock syndrome (DSS) at screening/baseline? [Yes; No] If yes, list symptoms
What is the subject's childbearing potential? [Of Childbearing Potential; Permanently Sterilized; Postmenopausal; Premenarchal]
Does the subject have any history of Tobacco/Nicotine use? [Yes; No] If yes, Type of substance – Usage – Amount – Unit - Frequency

5.1.7. Exposure

Table 4 presents the list of exposure to study treatment that will be reported in the patient profiles. The exposure will additionally be graphically presented in the patient profiles where different colors are used for different dose levels.

Table 4 – Exposure

Variables listed in patient profile
Name of actual treatment [Placebo; JNJ-64281802]
Start date/time of treatment
Dose with unit; dose form; route and frequency

5.1.8. Protocol Deviations

A listing will be created for the major protocol deviations.

5.1.9. Concomitant Medications

Medications taken from the date when the main study ICF is signed through the end of study will be reported (see Appendix 3 for a more complete definition of concomitant medications). In the patient profiles concomitant therapy will be displayed by indication:

- Adverse Event (AE number and term)
- Medical History (Medical history number and term)
- Prophylaxis
- Trial Indication – Dengue Fever
- Other

Table 5 presents the list of the concomitant medications variables that will be reported in the patient profiles.

Table 5 – Concomitant Medications

Variables listed in patient profile
Medication or Therapy preferred term using the World Health Organization-Drug Dictionary (WHO-DD)
Start date (study day) and end date (study day) or ongoing
Dose with unit; route and frequency

5.1.10. Medical History

Table 6 presents the list of the medical history variables that will be reported in the patient profiles.

Table 6 – Medical History

Variables listed in patient profile
Has the subject experienced any past and/ or concomitant diseases? [Yes; No] If yes, list the medical history body system and term, start and end date

5.2. Participant Dispositions

Table 7 presents the list of disposition variables that will be reported in the patient profiles.

Table 7 – Baseline Characteristics

Variables listed in patient profile
Date and time (study day) of signature on informed consent
Eligibility criteria met [Yes; No] If no, criterion
Date and time (study day) of randomization
Planned treatment group [Placebo; JNJ-64281802]
Date and time (study day) of discharge from the inpatient stay

Variables listed in patient profile
Completed the study treatment [Yes, Completed (date/ study day); No, Discontinued (date/ study day)] If no, reason for treatment discontinuation If withdrawal by subject - Lost to follow-up - Withdrawal of consent or ascent - Death - Other: specify
Completed the study [Yes, Completed (date/ study day); No, Discontinued (date/ study day)] If no, reason for study discontinuation If withdrawal by subject - Lost to follow-up - Withdrawal of consent or ascent - Death - Other: specify

5.3. Efficacy Endpoint(s) analysis

Given the small number of participants enrolled, no efficacy analysis will be performed in terms of hypothesis testing, descriptive statistics, mean plots, etc. The efficacy variables presented in the patient profiles are provided in Table 8. For selected virological parameters graphical representations will be created (Table 8).

Table 8 – Efficacy analysis

Virological Variables	
Plot over time in patient profiles (all collected values will be displayed)	
DENV RT-qPCR viral load (copies/mL)	Only the DENV serotype results with at least one detectable value will be presented. It will be indicated in the patient profile with which DENV serotype the patient has been infected. Results will be presented on log_{10} scale.
DENV NS1 serum protein levels (Panbio units)	It will be indicated in the patient profile with which DENV serotype the patient has been infected.
Anti-DENV IgM antibody response (Panbio units)	It will be indicated in the patient profile with which DENV serotype the patient has been infected.
Anti-DENV IgG [direct] antibody response (Panbio units) Anti-DENV IgG [indirect] antibody response (Panbio units)	It will be indicated in the patient profile with which DENV serotype the patient has been infected.
Listed in patient profiles (all collected values will be displayed)	
Anti-DENV neutralizing antibody response (PRNT50)	For all DENV serotypes, the PRNT50 titer values will be shown at screening/baseline and at Day 28 visit.
Spaghetti plot over time (all collected values will be displayed)	
DENV RT-qPCR viral load (copies/mL)	Only the DENV serotype results with at least one detectable value will be presented. A solid line is used for patients randomized to JNJ-64281802 and a dashed line is used for patients randomized to placebo. Different symbols and colors are used to distinguish each participant. Patient IDs together with DENV serotype will be shown. A horizontal line will be show at LLOQ value. Results will be presented on log_{10} scale.

DENV NS1 serum protein levels (Panbio units)	A solid line is used for patients randomized to JNJ-64281802 and a dashed line is used for patients randomized to placebo. Different symbols and colors are used to distinguish each participant. Patient IDs together with DENV serotype will be shown. A horizontal line will be show at the negative (<9 Panbio units) and positive (>11 Panbio units) interpretation line.
Anti-DENV IgM antibody response (Panbio units)	A solid line is used for patients randomized to JNJ-64281802 and a dashed line is used for patients randomized to placebo. Different symbols and colors are used to distinguish each participant. Patient IDs together with DENV serotype will be shown. A horizontal line will be show at the negative (<9 Panbio units) and positive (>11 Panbio units) interpretation line.
Anti-DENV IgG [direct] antibody response (Panbio units) Anti-DENV IgG [indirect] antibody response (Panbio units)	A solid line is used for patients randomized to JNJ-64281802 and a dashed line is used for patients randomized to placebo. Different symbols and colors are used to distinguish each participant. Patient IDs together with DENV serotype will be shown. For direct IgG antibody response, a horizontal line will be show at the negative (<18 Panbio units) and positive (>22 Panbio units) interpretation line. For indirect IgG antibody response, a horizontal line will be show at the negative (<9 Panbio units) and positive (>11 Panbio units) interpretation line. Separate graphs are created for direct and indirect anti-DENV IgG antibody responses.
Barplot per patient	
Anti-DENV neutralizing antibody response (PRNT50)	The PRNT50 titer values will be shown in a barplot per patient by DENV serotype and visit (screening/baseline and Day 28). Treatment information and DENV infection serotype will be indicated in the plot.
Dengue Specific Signs and Symptoms	
DENV-Infection Associated Adverse Events	For each sign/symptom it is listed in the patient profile whether it occurred or not. If yes, report the date (study day) of first and last occurrence.

Per participant, an overlay graph will be created showing the following virological parameters over time: DENV RT-qPCR viral load; DENV NS1 serum protein levels; anti-DENV IgM antibody response; anti-DENV IgG [direct] antibody response; and anti-DENV IgG [indirect] antibody response. Treatment information will be indicated in the graph.

Combined graphs of virological variables and DENV-infection specific signs/symptoms (DENV-Infection Associated Adverse Events) could be created, if deemed useful.

DENV RT-qPCR viral load

Serum DENV RT-qPCR viral load will be assessed using a validated quantitative DENV RT - qPCR assay. Limits of detection (LOD) and lower limit of quantification (LLOQ) for each of the 4 serotypes on this assay are:

Serotype	DENV Parameter	LOD	LLOQ	Imputed values	
				LOD	LLOQ
DENV-1	RT-qPCR (copies/mL)	29	1000	14.5	500
	RT-qPCR (log_{10} copies/mL)	1.46	3.00	1.16	2.70
DENV-2	RT-qPCR (copies/mL)	60	1000	14.5	500
	RT-qPCR (log_{10} copies/mL)	1.78	3.00	1.16	2.70
DENV-3	RT-qPCR (copies/mL)	36	1000	14.5	500
	RT-qPCR (log_{10} copies/mL)	1.56	3.00	1.16	2.70
DENV-4	RT-qPCR (copies/mL)	55	1000	14.5	500

	RT-qPCR (log_{10} copies/mL)	1.74	3.00	1.16	2.70

Log_{10} values rounded to 2 decimals.

For analysis purposes, the following imputations will be done for results below LOD or LLOQ:

- if the result is 'TARGET NOT DETECTED' (i.e., below LOD), the value will be imputed with the minimum over the four serotypes of LOD/2 (copies/mL);
- if the result is 'TARGET DETECTED' (i.e. below LLOQ), the value will be imputed with LLOQ/2 (copies/mL) (values with <LLOQ will always be imputed even if a value is available).

5.4. Safety Analyses

5.4.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The following information for each adverse event will be provided in the patient profiles. The adverse events will be sorted by start date/time in the patient profiles.

- Preferred term/System organ class
- Start date/time (study day)
- End date/time (study day)
- Ongoing [Yes; No]
- Toxicity grade
- Serious [Yes; No]
- Outcome [Fatal; Not Recovered or Not Resolved; Recovered or Resolved; Recovered or Resolved with Sequelae; Recovering or Resolving]
- Relationship to study treatment [Related; Not Related]
- Action taken with study treatment [Drug Interrupted; Dose Not Changed; Dose Reduced; Drug Withdrawn; Not Applicable]
- Other action taken
- Concomitant or additional therapy [Yes; No]

A plot over time of the AEs will be presented in the patient profiles. Information will include the preferred term. Different colors are used for the toxicity grades, and a symbol is used to identify any serious adverse event.

5.4.2. Additional Safety Assessments

5.4.2.1. Clinical Laboratory Tests

Toxicity grades will be computed according to the United States Food and Drug Administration Toxicity Grading as presented in appendix 6 of the protocol. In case different grades are available for fasted/non-fasted results, the results are assumed to be taken in the condition as specified in the protocol (i.e. not necessarily according to possible remarks indicating a deviation to this). If no

condition is specified in the protocol, the non-fasting gradings should be used. In case no toxicity grades are defined for any laboratory test, then non-graded abnormalities (high/low vs. normal range) will be used instead.

Hematology and Chemistry laboratory tests will be plotted over time (days since first drug intake). All collected values will be displayed. In case of a toxicity/abnormality, the toxicity/abnormality will be flagged with the actual value on the plot.

- Different colors are used for toxicity grades 0-4, and different colors are used for below the lower limit of normal / normal / above the lower limit of normal.
- Different symbols are used for graded vs. non-graded laboratory tests.
- Normal ranges will be indicated for each laboratory test.

5.4.2.2. Vital Signs and Physical Examination Findings

The vital sign parameters that will be analyzed are temperature, pulse, systolic blood pressure, diastolic blood pressure, respiratory rate, oxygen saturation and I/O ratio.

Toxicity grades for the vital signs will be computed according to the United States Food and Drug Administration Toxicity Grading as presented in Table 9 (and appendix 6 of the protocol). No toxicity grades/abnormalities are defined for oxygen saturation and I/O ratio.

Vital signs will be plotted over time (days since first drug intake). All collected values will be displayed. In case of a toxicity/abnormality, the toxicity/abnormality will be flagged with the actual value on the plot.

- Different colors are used for toxicity grades 0-4.
- Different symbols are used for the direction of the toxicity grade (below/above).
- Normal ranges will be indicated for each vital sign.

Table 9: Vital Signs: Abnormality Criteria

Vital Signs	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** Fever (°F) **	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	>40 >104.0
Pulse (bpm)				
Tachycardia	101-115	116-130	>130	
Bradycardia	50-54	45-49	<45	
Systolic blood pressure (mmHg)				
Hypertension (Systolic)	141-150	151-155	>155	
Hypotension (Systolic)	85-89	80-84	<80	
Diastolic blood pressure (mmHg)				
Hypertension (Diastolic)	91-95	96-100	>100	
Respiratory rate (breaths/minute)	17-20	21-25	>25	

Abnormal physical examination results will be listed in the patient profiles (date/time of examination, study day, body system, verbatim examination finding, clinically significant).

5.4.2.3. Electrocardiogram

The ECG parameters that will be analyzed are heart rate (HR), PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the Fridericia's formula (QTcF) correction method.

QTcF values will be used as reported in the database. In case these corrected QT intervals are not present in the database, these will be derived for analysis using the following formula, rounding results to the nearest integer:

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$.

Table 10 presents the abnormality criteria for the ECG parameters. No abnormality criteria are defined for RR interval.

Table 10: Criteria for Abnormal ECG parameters

Abnormality class and label	ECG parameter			
	HR (bpm)	**PR (msec)**	**QRS (msec)**	**QT, QTcF (msec)**
Abnormalities for actual values				
Low	< 45	-	-	-
High	> 100	> 220	≥ 110	> 450

ECG parameters will be plotted over time (days since first drug intake). All collected values will be displayed. In case of an abnormality, the abnormality (Low/High) will be flagged with the actual value on the plot.

- Different colors are used for normal vs abnormality.
- Different symbols are used for the direction of the abnormality (below/above).
- Normal ranges will be indicated for each parameter.

Electrocardiogram interpretation will be listed in the patient profiles. The date/time (study day), evaluator [Investigator; Central laboratory], result [Abnormal; Normal] will be provided. In case of abnormal, clinically significant [Yes; No] information will be provided.

5.5. Other Analyses

5.5.1. Pharmacokinetics

A listing of individual plasma concentrations of JNJ-64281802 (ng/ml) at each collected timepoint will be provided. All available values will be shown.

5.6. Interim Analyses

Not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
AUC	area under the curve
BMI	body mass index
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DENV	Dengue virus
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
HLA	human leukocyte antigen
ICF	informed consent form
Ig	Immunoglobulin
LLOQ	lower limit of quantification
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
VL	viral load
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

On 14-Sep-2023, the Sponsor decided to terminate study 64281802DNG2003 early due to low enrollment and not for any safety-related reasons. Five participants were enrolled into the study. The last enrollment was on 19-Sep-2022. It was decided to simplify and reduce the statistical outputs to listings and individual patient profiles because data of only five randomized participants were collected. Therefore, no summary statistics across participants will be produced, and data will be reported as a listing generated for each participant (patient profile) and clinical narratives. In addition, graphical representations will be created for selected virological parameters.

6.3. Appendix 3 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 continue on after the first dose of study intervention.

6.4. Appendix 4 Laboratory Toxicity Grading

Toxicity grades will be computed according to the United States Food and Drug Administration Toxicity Grading as presented in appendix 6 of the protocol.

7. REFERENCES

1. Low JG, Sung C, Wijaya L, et al. Efficacy and Safety of Celgosivir in Patients with Dengue Fever (CELADEN): A Phase 1b, Randomised, Double-blind, Placebo-controlled, Proof-of-concept Trial. Lancet Infect Dis. 2014.

2. Nguyen NM, Tran CHB, Phung LK, et al. A Randomized, Double-blind Placebo-controlled Trial of Balapiravir, a Polymerase Inhibitor, in Adult Dengue Patients. J Infect Dis.2013; 207(9); 1442-1450.

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