A Phase 2a, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Antiviral Activity, Safety, and Pharmacokinetics of Repeated Oral Doses of JNJ-64281802 Against Dengue Serotype 3 Infection in a Dengue Human Challenge Model in Healthy Adult Participants

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Table 1: Abbreviations

A1AG	Alpha-1 acid glycoprotein
ABV	alcohol by volume
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{plasma}	area under the JNJ-64281802 plasma concentration-time curve
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
C	capsid
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
cDNA	complementary deoxyribonucleic acid
CFR	Code of Federal Regulations
CHIM	Controlled Human Infection Model
CIR	Center for Immunization Research
CLIA	Clinical Laboratory Improvement Amendments
CPK	creatine phosphokinase
CRF	case report form(s)
CRIMSON	Clinical Research Information Management System of the NIAID
CRL	Charles River Laboratories
CSO	Clinical Safety Office
CV	coefficient of variation
DDT	Drug Development Team
DDUT	Drug Development Unblinded Team
DENV	dengue virus (serotypes DEN1, DEN2, DEN3, and DEN4)
DF	dengue fever
DHCM	dengue human challenge model
DHF	dengue hemorrhagic fever
DSMB	Data and Safety Monitoring Board
DMEC	Dengue Memory Enhancement Card
DNA	deoxyribonucleic acid
DSS	dengue shock syndrome
E	envelope protein of dengue virus
EC_{50}	median 50% effective concentration
ECG	electrocardiogram
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human choriogonadotropin
HCV	hepatitis C virus
HID_{50}	50% human infectious dose
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
CCI	[redacted]
HRT	hormonal replacement therapy
IB	investigator's brochure
IC_{50}	50% inhibitory concentration

ICF	**informed consent form**
ICH	**International Conference on Harmonisation**
ICMJE	**The International Committee of Medical Journal Editors**
ICS	**intracellular cytokine staining**
IDS	**Investigational Drug Service**
IgA,IgG,IgM,IgE	**immunoglobulins A, G, M, E**
IND	**investigational new drug**
INR	**international normalized ratio**
IRB	**Institutional Review Board**
ITT	**intent-to-treat**
IV	**intravenous**
JHSPH	**Johns Hopkins Bloomberg School of Public Health**
LD	**loading dose**
LID	**Laboratory of Infectious Diseases**
LLN	**lower limit of normal**
LLOQ	**lower limit of quantification**
M	**membrane protein of dengue virus**
MD	**maintenance dose**
MID_{50}	**50% mosquito infectious dose**
NIAID	**National Institute of Allergy and Infectious Diseases**
NIH	**National Institutes of Health**
NOAEL	**no observed adverse effect level**
NP	**nasopharyngeal**
NS	**non-structural**
NSAID	**non-steroidal anti-inflammatory drug**
OCRPRO	**Office of Clinical Research Policy and Regulatory Operations**
PBMC	**peripheral blood mononuclear cell**
PFU	**plaque-forming units**
PI	**principal investigator**
PK	**pharmacokinetics**
POCBP	**person of child-bearing potential**
PRNT	**plaque reduction neutralization titer**
PT/PTT	**prothrombin time/ partial thromboplastin time**
QTc	**corrected QT interval**
QTcB	**QT interval corrected using Bazett's formula**
QTcF	**QT interval corrected using Fridericia's formula**
REDCap	**Research Electronic Data Capture**
RNA	**ribonucleic acid**
SAE	**serious adverse event**
SAR	**suspected adverse reaction**
SC	**subcutaneous**
SD	**study day**
SLEV	**St. Louis encephalitis virus**
STD	**standard deviation**
SE	**standard error**
SRCP	**Safety Review and Communications Plan**
SDM	**site-directed mutants**
SUSAR	**serious and unexpected suspected adverse reaction**
t_{Max}	**the median time to maximum concentration**
T_{Max}	**maximum temperature in a 24-hour period**
TEAE	**treatment-emergent adverse event**
UGT	**uridine diphosphate-glucuronosyltransferase**
ULN	**upper limit of normal**
UP	**unanticipated problem**
USA	**United States of America**
UTR	**untranslated region**

VCD	**virologically-confirmed dengue**
VL	**viral load**
WBC	**white blood count**
WCG IRB	**Western Copernicus Group Institutional Review Board**
WHO	**World Health Organization**
Wt	**wild type**

1 Protocol Precis

Protocol Title:	A Phase 2a, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Antiviral Activity, Safety, and Pharmacokinetics of Repeated Oral Doses of JNJ-64281802 Against Dengue Serotype 3 Infection in a Dengue Human Challenge Model in Healthy Adult Participants.
Version:	v7.2
Version Date:	August 28, 2023
Version History:	v1.0 March 31, 2021 v2.0 June 8, 2021 v3.0 August 12, 2021 v4.0 December 22, 2021 v5.0 January 24, 2022 v6.0 April 13, 2022 v7.0 February 17, 2023
Phase:	Phase 2a
Principal Investigator:	PPD 
Subjects:	Healthy male and non-pregnant female subjects 18 to 55 years of age, inclusive, with no history of previous DENV or Zika virus infection.
Number of Subjects:	54
Study Design:	Placebo-controlled, double-blind study evaluating the ability of JNJ-64281802 to protect against infection with rDEN3Δ30 when JNJ-64281802 is administered beginning five days prior to challenge with rDEN3Δ30 and continued through Study Day 21 for Cohort 1. For Cohort 2, JNJ-64281802 is administered 2 days prior to challenge with rDEN3Δ30 and continued through Study Day 15 (weekly dose regimens) or Study Day 21 (daily dose regimen).

Table 2: Dosing Schedule

COHORT 1	NUMBER OF SUBJECTS (N)	PRODUCT	DOSE	DOSING DAYS
GROUP 1	10	JNJ-64281802[C]	600 mg LD/200 mg MD (high dose)	-5 to 21
	6	Placebo	Placebo	-5 to 21
	16	rDEN3Δ30	10^3 PFU	1
GROUP 2	6	JNJ-64281802[C]	40 mg LD/10 mg MD (low dose)	-5 to 21
	6	JNJ-64281802[C]	200 mg LD/ 50 mg MD (medium dose)	-5 to 21
	2	Placebo	Placebo	-5 to 21
	14	rDEN3Δ30	10^3 PFU	1
				TOTAL SUBJECTS COHORT 1: 30[A]

COHORT 2	NUMBER OF SUBJECTS (N)	PRODUCT	DOSE	DOSING DAYS
GROUP 3	6	JNJ-64281802[D]	800 mg BID LD / 250 mg MD (daily dosing)	-2 to 21
	2	Placebo	Placebo	-2 to 21
	8	rDEN3Δ30	10^3 PFU	1
GROUP 4	6	JNJ-64281802[D]	450 mg BID LD / 1200 mg MD (weekly dosing)	-2 to 1, 8, 15
	2	Placebo	Placebo	-2 to 1, 8, 15
	8	rDEN3Δ30	10^3 PFU	1
GROUP 5	6	JNJ-64281802[D]	250 mg BID LD / 500 mg MD (weekly dosing)	-2 to 1, 8, 15
	2	Placebo	Placebo	-2 to 1, 8, 15
	8	rDEN3Δ30	10^3 PFU	1
				SUBJECT TOTAL COHORT 2: 24[B]

LD = loading dose; MD = maintenance dose; PFU = plaque-forming units; BID = 2x per day

CCI [redacted]

A. In order to account for a potential early discontinuation, a maximum of 7 participants can be replaced in case of discontinuation before last dose of study drug on Day 21.
B. In order to account for a potential early discontinuation, a maximum of 6 participants can be replaced in case of discontinuation before Day 21
C. CCI [redacted]
D. CCI [redacted]

Investigational Product Descriptions:

JNJ-64281802 is a novel, potent, pan-serotypic small-molecule inhibitor of dengue virus (DENV) targeting DENV nonstructural protein (NS)4B. JNJ-64281802 is being developed for the prevention and treatment of dengue infection. CCI [redacted]

The "challenge" virus, rDEN3Δ30, is a live recombinant DENV-3 virus and will be administered subcutaneously at a dose of 3 $\log_{10}$ plaque-forming units (1,000 PFU).

Summary of primary study objectives:

- To assess the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV-3 ribonucleic acid (RNA).

Summary of secondary study objectives:

- To assess the safety and tolerability of JNJ-64281802.
- To assess the DENV infection-associated adverse events (AE).
- To assess the antiviral activity of JNJ-64281802 versus placebo on other virologic endpoints.
- To assess the pharmacokinetics (PK) of JNJ-64281802 following repeated oral dosing.
- To evaluate the relationship between the PK and the antiviral activity of JNJ-64281802.
- To assess the anti-DENV-3 immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody responses.

Exploratory Objectives:

- To determine the incidence of uncomplicated dengue infection.
- To explore the anti-DENV-3 neutralizing antibody response.
- To explore the anti-DENV-3 cellular immune response.
- To explore changes in serum protein levels (including cytokines).
- To explore the DENV-3 NS1 serum protein levels (Cohort 1; optional for Cohort 2).
- To explore the resistance of DENV-3 to JNJ-64281802.
- To explore the relationship between the PK and the safety and tolerability of JNJ-64281802.
- To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802.

Study Design:

The study follows an adaptive 2-stage design consisting of 2 cohorts, each with up to 3 groups. The 2 cohorts will be enrolled in a staggered manner. As a safety measure, a sentinel group of 4 participants will be enrolled in Cohort 1 (Group 1a) before enrolling the remaining participants (Group 1b and Group 2) in the cohort.

After providing written informed consent, subjects will undergo eligibility screening, including medical history, physical examination, hematology testing, liver and renal function testing, human immunodeficiency virus (HIV) screening, hepatitis B and C screening, urinalysis, urine toxicology, electrocardiogram (ECG), and serology screening for previous DENV and Zika virus infection.

Cohort 1: Serum/urine pregnancy testing will be performed on applicable persons of childbearing potential at multiple screening visits (if applicable) and on Study Day -5 prior to administration of study agent. An alcohol breath test may be administered (at PI/provider discretion) upon presentation to the unit on Study Day -6. Participants who are eligible, will be admitted to the inpatient unit on Study Day -6 through Study Day -4 during intensive PK sampling. Administration of JNJ-64281802 will begin on Study Day -5 and continue through Study Day 21. Receipt of challenge with rDEN3Δ30 inoculation will be scheduled for Study Day 1.

Cohort 2: Serology screening will also be performed for West Nile virus and St. Louis encephalitis virus (SLEV), in addition to DENV and Zika. Serum/urine pregnancy testing will be performed on applicable persons of childbearing potential at multiple screening visits (if applicable) and on Study Day -2 prior to administration of study agent. An alcohol breath test may be administered (at PI/provider discretion) upon presentation to the unit on Study Day -3. Participants who are eligible will be admitted to the inpatient unit on Study Day -3 through Study Day 1 during intensive PK sampling. Administration of JNJ-64281802 will begin on Study Day -2 and continue through Study Day 15 for the weekly dosing regimens or Study Day 21 for daily dosing regimen. Receipt of challenge with rDEN3Δ30 inoculation will be scheduled for Study Day 1.

The Cohort 2 regimens are based on the long t1/2 of the compound and the PK profile observed in Cohort 1, and the feasibility of weekly dose regimen will be assessed in the weekly dosing regimens.

Subjects will be evaluated according to the attached Schedule of Procedures. During the outpatient and inpatient visits through Study Day 22, the subjects will be evaluated by a clinician and will have blood drawn for clinical laboratory studies, virologic assays, and immunologic assays. Subjects will measure their temperatures (or have their temperatures taken onsite) and readings will be recorded twice a day from Study Day 1 through Study Day 29 (longer as needed).

Cohort 1: Subjects will be seen at the clinic for their only overnight stay from Study Day -6 to Day -4. Subjects will take study product at home on Day -3 and -2 and will be called those days to complete a brief phone visit. Subjects will come for in person clinic visits for dosing, blood draw and other study activities on Study Day -1, Day 1, and Day 3. A phone call will occur on Day 2 and Day 4. In-person clinic visits will occur on: Study Day 5, 7, 9, 11, 14, 16, 18, 21, 23, 25, and 29. Study day 21 will be another PK sampling period and thus will be a full day at the clinic with scheduled blood draws with no overnight stay. Telephone calls will occur Study Days -3, -2, 2, 4, 6, 8, 10, 12, 13 15, 17, 19, and 20 (more often as needed) as designated in Table 3 and section 7.16. Follow up visits will occur on Study Days 36, 43, 50, 57, 63, 70 and subjects will complete their final study visit on Study Day 85.

Cohort 2: Subjects will be seen at the clinic for their only overnight stay from Study Day -3 to Day 1. Subjects will come for in person clinic visits for dosing, blood draw and other study activities on Study Days 4, 6, 8, 11, 13, 15, 18, 21, 25, and 29. Study Day 15 (weekly dosing regimens) or Day 21 (daily dosing regimen) will be another PK sampling period and thus will be a full day at the clinic with scheduled blood draws with no overnight stay. Follow up visits for all participants will occur on Study Days 32, 36, 43, 57, 70 and subjects will complete their final study visit on Study Day 85. If participants have a positive DENV-3 qualitative PCR result on Day 25 and/or Day 32, additional in-person clinic visits will occur on Study Day 27 and/or 34 respectively, in addition to the days listed above. The schedule of procedures is provided in Table 4 and section 7.17.

Table 3: Schedule of Procedures – Cohort 1

	Screen[5]		Dosing Study Days (Inpatient visits marked in gray)																									Follow-up Study Days[4]									
Procedure	-65 to -6	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	25	29	36	43	50	57	63	70	85
In-Person Visit	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X	X	X	X
Phone call Visit					X	X			X		X		X		X		X		X	X		X		X		X	X											
Informed Consent	X																																					
COVID-19 screening questions	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X	X	X	X
DMEC review									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
NP or mid-turbinate nasal swab		[X][10]						[X][10]																				[X][10]											
Overnight Stay on Unit		X	X																																			
Study Drug Taken			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										
DENV-3 Inoculation								X																														
Physical exam	X[6]		X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X	X	X	X[6]
Vital Signs	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X	X	X	X
Complete Medical History	X																																					
Collection of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgE[12]			X					X		X*		X*		X*		X*		X*			X*		X*		X*			X*										
PK Analysis			X[2]	X				X						X		X		X					X					X[13]	X	X	X				X		X	X
Quantitative RT-PCR							X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X	X	X	X
Qualitative RT-PCR																															X[3]	X	X	X	X	X	X	X
Plaque Assay							[X]	[X]		[X]		[X]		[X]		[X]		[X]			[X]		[X]		[X]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
NS1 ELISA							X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X	X	X	X
IgG & IgM ELISA			X					X										X			X		X		X			X	X	X	X	X	X		X			X
Neutralizing Antibody								X										X							X			X			X							X
Serum Protein Analysis			X							X						X					X				X							X						X
Viral Genome Sequencing														[X]		[X]		[X]			[X]		[X]		[X]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
PBMC isolation			X													X							X								X							X
Host RNA Analysis			X							X						X					X				X								X					X
HLA Genotyping & Pharmacogenomics			X																																			
CMP																		X							X						X				X			
Chemistry Panel[9]	X		X				X					X																	X									
CBC with differential	X		X				X					X						X							X				X		X				X			
PT/PTT	X		X				X					X						X							X				X		X				X			
HIV, HCV, HBV	X																																					
Denv/Zikv screening	X																																					
Pregnancy Test[1]	X		X					X																				X			X							X
FSH Test[11]	X																																					

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	Screen[5]		Dosing Study Days (Inpatient visits marked in gray)																									Follow-up Study Days[4]									
Procedure	-65 to -9	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	25	29	36	43	50	57	63	70	85
Urinalysis & Urine toxicology Screen	X																																				
Alcohol Breath Test		X[14]																																			
12-lead ECG[8]	X		X					X																				X									X

Aes = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PT/PTT = prothrombin time/partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction

1. Serum or urine pregnancy testing only performed for persons of childbearing potential..
2. On SD -5: 7 PK samples will be collected during 16-hour window.
3. Qualitative RT-PCR will be performed on samples collected on **Days 29, 36, 43, 50, 57, 63, 70, and 85.** If the participant is DENV-3 positive detected for first time at Day ≥29, qualitative RT-PCR will be performed **twice weekly (preferably with 3 to 4 days in between samples)** until the participant results are negative and until resolution of DENV infection-associated Aes. Participants who are DENV-3 positive on Day 85 should return for additional clinical and virologic assessments until the participant results are negative and until resolution of DENV infection-associated Aes. Additional testing using different nucleic acid based methods for the detection and/or quantification of DENV-3 may be performed.
4. Phone calls to collect time of dose, time of last food, AE's, and concomitant therapy on SD -3, -2, 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, and 20.
5. Screening may occur over multiple visits. Certain procedures must be performed within different time frame relative to dosing, see Section 7.1. Screening window is Day -65 to Day -6.
6. A complete physical exam will be performed at screening and on Day 85. At all other indicated timepoints a focused physical exam will be performed.
7. [X] Sample will be collected, but test will only be performed if indicated by guidelines in the protocol.
8. **ECGs are recorded pre-dose on dosing days.**
9. Chemistry panel consists of sodium, potassium, chloride, bicarbonate, BUN, calcium, phosphate, albumin, total protein, total cholesterol, creatinine, glucose, AST, ALT, GGT, HDL cholesterol, LDL cholesterol, triglycerides, magnesium, calculated creatine clearance (by MDRD), lipase, amylase, total bilirubin, alkaline phosphatase, uric acid
10. Nasopharyngeal (NP) or mid-turbinate swab to test for SARS-CoV 2 – the virus that causes COVID-19 – will be collected from all volunteers regardless of vaccination status based on guidance from federal, state, local, and/or institutional health officials* or at the discretion of the clinician (may be collected up to 72 hours in advance of stated collection time).
    *This guidance may be informed by the local COVID infection rate, severity of infections, vaccination rates, and other factors as the COVID-19 pandemic continues to evolve and change. NP or mid-turbinate swabs may be collected at other time-points if volunteer has COVID-like symptoms.
11. FSH performed only in females who have stopped menstruating for > 12 consecutive months but < 24 months. (Anyone who has had amenorrhea > 24 consecutive months is considered postmenopausal and does not require FSH).
12. In participants who develop a rash, an additional sample will be collected at onset of rash and tested. Noted on this chart with an asterisk {X*}
13. On Study Day 21: 6 PK samples will be collected during a 12-hour window
14. Alcohol breath test may be performed at the discretion of PI/provider upon admission to inpatient unit

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Table 4: Schedule of Procedures - Cohort 2

	Screen[5]	Inpatient Stay				Clinic Visits During Dosing Window(s) D=Daily Dosing Group; W=Weekly Dosing Groups										Follow-up Clinic Visits (Day 27 and 34 only if indicated[16])									
Procedure	**-62 to -3**	**-3**	**-2**	**-1**	**1**	**4**	**6**	**8**	**11**	**13**	**15D**	**15W**	**18**	**21D**	**21W**	**25**	**27**	**29**	**32**	**34**	**36**	**43**	**57**	**70**	**85**
In-Person Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X																								
COVID-19 screening questions	X	X																							
DMEC review						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
NP or mid-turbinate nasal swab [7, 10]		[X]												[X]	[X]										
Overnight Stay on Unit		X	X	X																					
Study Drug Taken at Clinic (Daily Dose Regimen)			X	X	X	X	X	X	X	X	X		X	X											
Study Drug Taken at Clinic (Weekly Dose Regimen)			X	X	X			X				X													
DENV-3 Inoculation					X																				
Physical exam	X[6]		X	X	X	X	X	X	X	X	X	X		X	X		X					X	X	X	X[6]
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Medical History	X																								
Collection of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgE [12]			X		X	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*											
PK Analysis [2]			X[2]	X	X	X		X	X		X[2]	X[2]	X	X[2]	X[2]	X		X				X	X		X
A1AG			X	X	X	X		X	X			X	X	X		X		X				X	X	X	X
Quantitative RT-PCR				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative RT-PCR														X	X	X[3]	X	X	X	X	X	X	X	X	X
Plaque Assay [7]				[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
NS1 ELISA [4]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgG & IgM ELISA			X		X				X	X	X	X	X	X	X			X	X	X		X			X
Neutralizing Antibody [14]			X		X																	X			X
Serum Protein Analysis			X			X		X		X			X									X			X
Viral Genome Sequencing [15]								[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
PBMC isolation			X					X			X	X		X	X			X							X
Host RNA Analysis			X			X		X		X			X												X
HLA Genotyping & Pharmacogenomics			X																						
CMP									X				X					X					X		
Chemistry Panel [9]	X		X	X			X																		
CBC with differential	X		X	X			X		X				X					X					X		
PT/PTT	X		X	X			X		X				X					X					X		
HIV, HCV, HBV	X																								
Dengue/Zika/West Nile/SLEV screening	X																								
Pregnancy Test [1]	X		X		X									X	X			X							X
FSH Test [11]	X																								

CIR 332

	Screen[5]	Inpatient Stay				Clinic Visits During Dosing Window(s) D=Daily Dosing Group; W=Weekly Dosing Groups										Follow-up Clinic Visits (Day 27 and 34 only if indicated[16])									
Procedure	**-62 to -3**	**-3**	**-2**	**-1**	**1**	**4**	**6**	**8**	**11**	**13**	**15D**	**15W**	**18**	**21D**	**21W**	**25**	**27**	**29**	**32**	**34**	**36**	**43**	**57**	**70**	**85**
Urinalysis & Urine toxicology Screen	X																								
Alcohol Breath Test		X[13]																							
12-lead ECG [8]	X		X		X						X	X		X	X										X

AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PT/PTT = prothrombin time/partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction; A1AG = alpha-1 acid glycoprotein

1. Serum or urine pregnancy testing only performed for persons of childbearing potential..
2. On SD -2 : 7 PK samples will be collected during 16-hour window: within the 2 hours prior to dosing with JNJ-64281802 as well as 1, 2, 4, 8, 12 (prior to second loading dose), 16 hours after dosing.
   On Study Day 15 for the weekly dosing regimen and on Day 21 for the daily dosing regimen: 6 PK samples will be collected during a 12-hour window: within the 2 hours prior to dosing with JNJ-64281802 as well as 1, 2, 4, 8, and 12 hours after dosing. On Day 21 for the weekly dosing regimen and Day 15 for the daily dosing and all other study days where PK samples are collected, a single blood collection will occur prior to dosing with JNJ-64281802 (if applicable).
3. Qualitative RT-PCR will be performed on samples collected on **Days 25, 27, 29, 32 , 34, 36, 43, 57, 70, and 85.** If a participant is DENV-3 positive detected at Day ≥25 (or day 23 if 25 is not available), qualitative RT-PCR for the set of participants enrolled in the same group and who were enrolled at the same day or later, will be performed on **days 27 and day 34** until the result participant results are negative and until resolution of DENV infection-associated AEs. Participants who are DENV-3 positive on Day 85 should return for additional clinical and virologic assessments until the participant results are negative and until resolution of DENV infection-associated AEs. Additional testing using different nucleic acid based methods for the detection and/or quantification of DENV-3 may be performed.
4. Analysis is optional, but samples need to be collected.
5. Screening may occur over multiple visits. Certain procedures must be performed within different time frame relative to dosing, see Section 7.1. Screening window is Day -62 to Day -2.
6. A complete physical exam will be performed at screening and on Day 85. At all other indicated timepoints a focused physical exam will be performed.
7. [X] Sample will be collected, but test will only be performed if indicated by guidelines in the protocol.
8. **ECGs are recorded pre-dose on dosing days.**
9. Chemistry panel consists of sodium, potassium, chloride, bicarbonate, BUN, calcium, phosphate, albumin, total protein, total cholesterol, creatinine, glucose, AST, ALT, GGT, HDL cholesterol, LDL cholesterol, triglycerides, lipase, amylase, total bilirubin, alkaline phosphatase, uric acid
10. Nasopharyngeal (NP) or mid-turbinate swab to test for SARS-CoV-2 will be collected from all volunteers regardless of vaccination status based on guidance from federal, state, local, and/or institutional health officials* or at the discretion of the clinician (may be collected up to 72 hours in advance of stated collection time).
    *This guidance may be informed by the local COVID infection rate, severity of infections, vaccination rates, and other factors as the COVID-19 pandemic continues to evolve and change. NP or mid-turbinate swabs may be collected at other time-points if volunteer has COVID-like symptoms.
11. FSH performed only in females who have stopped menstruating for > 12 consecutive months but < 24 months. (Anyone who has had amenorrhea > 24 consecutive months is considered postmenopausal and does not require FSH).
12. In participants who develop a rash, an additional sample will be collected at onset of rash and tested. Noted on this chart with an asterisk {X*}
13. Alcohol breath test may be performed at the discretion of PI/provider upon admission to inpatient unit
14. D -2 to be taken predose. Analysis is optional, but samples need to be collected.
15. Sequencing conducted only if DENV RNA positive.
16. In-person clinic visits with sample collection will only occur on Study Day 27 and/or 34 if the DENV-3 qualitative PCR results on Day 25 and/or Day 32, respectively, are positive.

2 Introduction

2.1 Background - Dengue

Dengue is caused by any of the 4 antigenically distinct dengue virus (DENV) serotypes (DENV-1, -2, -3, and -4), which belong to the genus *Flavivirus* in the family of the *Flaviviridae*. The DENVs are human pathogens which are transmitted through the bite of an infected female mosquito of the genus *Aedes*, mainly of the species *Aedes aegypti* and to a lesser extent *Aedes albopictus* [1]. Dengue is endemic in more than 125 countries, and has also again become endemic in the United States of America (USA) and its territories [2]. About half of the global population is currently at risk of becoming infected with DENV [3, 4]. According to the World Health Organization (WHO), dengue is among the top 10 threats to global health in 2019 [5].

The actual numbers of dengue cases are under reported and many cases are misclassified as other febrile illnesses such as malaria. It is estimated that there are 390 million DENV infections globally per year, of which 96 million manifest clinically (with any severity of the disease) [3]. On average, each year about 500,000 dengue cases require hospitalization due to severe and life-threatening disease and up to 25,000 patients die due to dengue.

During a primary DENV infection, approximately 75% of the individuals remain asymptomatic [6]. Those who show clinical symptoms mainly develop an acute, self-limiting febrile illness. The first clinical symptoms occur 3 to 8 days after a bite by a DENV-infected and viremic mosquito. Resolution of infection usually occurs within 4 to 7 days due to a robust innate and adaptive immune response [7]. A smaller percentage of DENV infections result in severe dengue outcomes such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Secondary DENV infections or infections with particularly virulent viral strains are thought to be associated with an increased risk for severe dengue [8].

During classical dengue fever (DF), an abrupt onset of fever is accompanied by a wide range of potential symptoms, ie, myalgia, arthralgia, headache, and rash; with retro-orbital pain and lower back pain being prototypical symptoms. Also vomiting, nausea, and anorexia are common [9]. During this febrile phase, those that will progress to severe or remain non severe cannot be distinguished. The critical phase is characterized by an increased propensity for capillary leakage and hemorrhage, typically manifested by scattered petechiae, hematuria, and gastrointestinal hemorrhage [7, 10]. Without early diagnosis and proper management, some patients experience shock from plasma leakage or less commonly blood loss, which can result in a sudden deterioration of the patient's condition [10].

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

In December 2015, the first vaccine against DENV was licensed in Mexico. The chimeric yellow fever – DENV tetravalent dengue vaccine (CYD-TDV; Dengvaxia®) is a live attenuated vaccine developed by Sanofi Pasteur. By November 2016, the vaccine had been approved for use in 18 countries including Brazil, Mexico, El Salvador, Costa Rica, and the Philippines. In late 2017, the vaccine was withdrawn again from the Philippian market because of safety concerns, which led to revocation of the vaccine's licensure in the Philippines in February 2019. In May 2019, the vaccine was approved in the USA for the prevention of dengue disease caused by all DENV serotypes (DENV-1, -2, -3, and -4) in individuals, 9 through 16 years of age, who have laboratory confirmed previous dengue infection and who live in endemic areas. The widespread use of the vaccine, however, is not foreseen per the WHO working group for immunization, as a number of factors need further consideration [11]. The Strategic

Advisory Group of Experts recommended countries to consider the introduction of Dengvaxia® only in geographic settings (national or subnational) with high dengue endemicity.

During recent years, drugs developed for prophylactic use are slowly getting more attention as potential alternatives to prevent dengue [12]. Prophylaxis could be beneficial for travelers to dengueendemic regions (eg, aid workers, tourists, business and military travelers, and expatriates), as well as for vulnerable populations living in endemic regions. By preventing viremia and/or by reducing viral load, DENV infection-associated morbidity and mortality could be reduced remarkably or even prevented [12]. In addition, an efficacious and safe prophylactic anti-DENV compound could potentially also be used as a therapeutic agent.

JNJ-64281802 is a novel anti-DENV small molecule targeting DENV NS4B. It has shown potent antiviral activity across all 4 DENV serotypes in nonclinical studies [13]. A Phase 1 first-in-human study 64281802DNG100 has been performed. A summary of the results is provided in section 2.2.

This is a Phase 2a study utilizing a dengue human challenge model (DHCM) in which healthy adult participants are inoculated with a recombinant DENV-3 strain, rDEN3Δ30, 5 days after initiation of daily dosing with JNJ-64281802 or placebo (ie, administered as pre-exposure prophylaxis). The aim of the study is to assess the antiviral activity of JNJ-64281802 in a prophylactic setting, and to examine the safety, tolerability, pharmacokinetics (PK), and the relationship between the PK and the antiviral activity of repeated oral doses of JNJ-64281802, compared with placebo. This study is intended to inform the prophylactic development program for JNJ-64281802, including clinical studies to assess the efficacy of JNJ-64281802 to prevent DENV infection.

2.2 Background - JNJ-64281802

2.2.1 Non-Clinical Studies

2.2.1.1 *Primary Pharmacology*

JNJ-64281802 is a novel anti-DENV small-molecule targeting DENV NS4B.

JNJ-64281802 showed potent in vitro antiviral activity against DENV irrespective of serotypes and genotypes. The median 50% effective concentration (EC50) was 0.05 nM with a selectivity index of 48,000 against DENV-2/16681/eGFP in Vero cells. In the presence of 50% human serum, the antiviral activity of JNJ-64281802 against DENV-2/16681/eGFP decreased 28-fold. JNJ-64281802 showed overall potent antiviral activity against all 4 DENV serotypes (lab-adapted strains and clinical isolates) with sub-nanomolar or low nanomolar median EC50 values against most strains and has a high specificity towards DENV.

The in vitro resistance profile and the molecular target of JNJ-64281802 was characterized using in vitro selection experiments in Vero cells infected with the DENV-2/Rega strain or the CCI CCI and SDMs analyses. Several mutations within the NS4B protein were observed. The activity of JNJ-64281802 against mutant DENV-2/16681 in the transient replicon assay was reduced 11- to 490-fold compared to wild type (WT; EC50 = 0.3 nM) when the tested DENV-2/16681 harbored the single mutation CCI, V91A, L94F, CCI, T108I, CCI or F237Y in the NS4B protein, or the double mutations CCI in the NS4B protein. CCI The emergence of mutations within the NS4B protein and the reduced activity of JNJ-64281802 conferred by these NS4B mutations, suggest NS4B as being the target of JNJ-64281802.

In DENV-2 inoculated mice treated with JNJ-64281802, dose-dependent viral ribonucleic acid (RNA) reductions in serum [redacted] compared with vehicle treated mice were observed and were associated with a significant effect on survival. In a non-human primate model, no viral RNA was detected at the highest doses of JNJ-64281802 ([redacted] 3 mg/kg/dose) against DENV-2/16681 and at the dose of 6 mg/kg against DENV-1/45AZ5 given prophylactically, indicating that JNJ-64281802 is highly effective in preventing infection after DENV challenge in this rhesus monkey model.

2.2.1.2 *Secondary Pharmacology*

[redacted]

2.2.1.3 *Safety Pharmacology*

[redacted]

2.2.1.4 *Pharmacokinetic and Metabolic Profile*

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

2.2.1.5 *Toxicology*

CCI [redacted]

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.2 Previous Human Experience with JNJ-64281802

The Phase 1 first-in-human study 64281802DNG1001 has evaluated the safety, tolerability, and PK of increasing single and multiple oral doses of JNJ-64281802 in a total of 122 healthy adult participants (ie, 39 participants in the single ascending dose part, 47 participants in the multiple ascending dose part, and 36 participants in the oral bioavailability part).

2.2.2.1 *Safety*

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

CCI

[redacted]

[redacted]

[redacted]

2.2.2.2 *Human Pharmacokinetics*

64281802DNG1001 (DNG1001)

Following single-dose administration with JNJ-64281802 (50-1,200 mg), formulated as oral solution, the exposure increased dose proportionally from 50 to 150 mg and less than dose proportionally from

240 to 1,200 mg, while following multiple dosing the exposure of JNJ-64281802 increased closer to dose proportionally over the investigated dose range (50 to 560 mg) compared with single dosing.

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

CCI

[redacted]

64281802DNG1004 (DNG1004)

CCI

[redacted]

64281802DNG1005 (DNG1005)

CCI

[redacted]

64281802DNG1006 (DNG1006)

CCI [redacted]

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

2.3 Background - Dengue Human Challenge Model with a Recombinant DENV-3 Strain

The DENV-3 DHCM to be used in study 64281802DNG2002 (further referred to as DNG2002) uses rDEN3Δ30 which was derived from DENV-3 Sleman/78. During the initial outbreak of the parent strain, DENV-3 Sleman/78 in Java, the illness observed was far more mild than previous DENV-3 infections and indeed less severe compared with another DENV-3 strain, Bantul, which was circulating at the same time. The majority of those infected had only fever and non-specific constitutional symptoms, with very few severe cases and no deaths associated with infection with DENV-3 Sleman/78. Epidemiologic investigations of the DENV-3 Sleman outbreak led investigators to conclude that this was a naturally attenuated virus and would be a good candidate for vaccine development [14]. rDEN3Δ30 was originally developed by the National Institutes of Health (NIH) as a live attenuated vaccine for the prevention of illness due to DENV-3. It was modified by a 31-nucleotide deletion in the 3′ untranslated region (UTR) of the parent strain of DENV-3 Sleman/78 and was therefore designated rDEN3Δ30 [15]. However, in preclinical studies of rDEN3Δ30 in non-human primates, rDEN3Δ30 was not attenuated compared with its wild-type parent virus (section 2.3.1). For this reason, it was abandoned as a candidate vaccine and repurposed as a virus to be used in dengue controlled human infection studies. In first evaluation of rDEN3Δ30 in humans, the viremia and reactogenicity data, particularly the rash, indicated the virus was more suitable as a challenge virus (section 2.3.3). The virus has been evaluated or utilized as a challenge virus in three human clinical trials (Table 6).

2.3.1 Studies of DENV-3 in Rhesus Monkeys

The replication (viremia), immunogenicity, and protective efficacy of DENV-3 were studied in rhesus monkeys. Monkeys inoculated with the wt DENV-3 Sleman/78 were viremic for 2.5 days, with a mean peak titer of 2.0 $\log_{10}$ PFU/mL. A significant difference was not found in the mean peak titer of viremia or the duration of viremia induced by wt DENV-3 Sleman/78, the recombinant parent virus rDEN3, and rDEN3Δ30 (Table 5) indicating that rDEN3Δ30 was not attenuated compared to the wildtype and recombinant parent viruses DENV-3 Sleman/78.

Table 5: Replication and Immunogenicity of DENV-3 in Rhesus Monkeys

	Dose (log_{10} PFU/mL)	% with Viremia	Mean No. of Viremic Days per Monkey	Mean Peak Virus Titer (log_{10} PFU/mL ± SE)	Geometric Mean Serum-Neutralizing Antibody Titer
DENV-3 Slemen/78	5	75	2.5	2.0 ± 0.4	325
rDEN3	5	100	2.3	1.4 ± 0.2	363
rDEN3Δ30	5	100	2.0	1.5 ± 0.2	265

2.3.2 Mosquito Transmissibility of rDEN3Δ30

The parent virus of the rDEN3Δ30 challenge virus, DENV-3 Sleman/78, is poorly transmitted to mosquitoes. Ingestion of 4.1 log_{10} PFU of wt DENV-3 Sleman/78 by *A. aegypti* mosquitoes infected the midgut of only 4 of 28 (14%) of mosquitoes tested and disseminated from the midgut in only 2 of 28 (7%) mosquitoes. The DEN3Δ30 virus demonstrated similar infectivity compared to the parent strain, DENV-3 Sleman/78 in mosquitoes [15]. The required dose of wt DENV-3 Sleman/78 exceeds 5 log_{10} PFU/mL in blood to allow for transmission to *A. aegypti* mosquitoes, the natural vector of dengue virus. As described below (section 2.3.3), the mean peak titer achieved by rDEN3Δ30 in infected volunteers is < 2 log_{10} PFU/mL, several log_{10} below that required for transmission. For these reasons, rDEN3Δ30 does not pose a risk for transmission and all clinical trials have been conducted as outpatient studies throughout the year. For more details on the nonclinical and clinical information regarding rDEN3Δ30, refer to the rDEN3Δ30 Investigator's Brochure (IB).

2.3.3 Clinical Experience with rDEN3Δ30

The DENV-3 challenge virus rDEN3Δ30 has been studied in 3 separate clinical trials (Table 6). The use of the different doses is explained below. All 3 studies were approved for and conducted ***as outpatient studies without seasonal restrictions***. More than 80 subjects have been inoculated with rDEN3Δ30 (40 of whom were flavivirus-naïve) and transmission of the virus to a third party has not occurred. See section 2.3.2 for a more detailed discussion of the poor transmissibility of this virus.

Table 6: Protocols rDEN3Δ30 was administered

CIR protocol number	Clinicaltrials.gov number	IND number	Dose administered (log_{10} PFU)
304	NCT02684383	16765	3
309	NCT02873260	15753	4
323	NCT03416036	15753	3

The clinical response to rDEN3Δ30 in flavivirus-naïve adults compared with placebo is presented in Table 7. Volunteers in CIR309 and 323 served as their own controls (they received placebo at dose 1 and were challenged 6 months later with rDEN3Δ30). In CIR304, rDEN3Δ30 was given to 10 volunteers and placebo was given to 4 volunteers. For this analysis, the clinical response of all volunteers who received rDEN3Δ30 as a challenge virus is combined for statistical power. Fever was observed in only 2 volunteers (5.0%). The fever lasted less than 24 hours in both volunteers. The incidence of rash, neutropenia, thrombocytopenia, myalgia, and retro-orbital pain occurred in significantly higher in volunteers who received rDEN3Δ30 compared to placebo (multiple comparisons correction not performed). The results of each individual study are described below.

2.3.3.1 *Study CIR 304*

In study CIR304, 14 healthy flavivirus-naïve adults were enrolled and randomly assigned to receive either rDEN3Δ30 or placebo. Ten participants received 3 $\log_{10}$ PFU of rDEN3Δ30 and 4 received placebo. All 10 rDEN3Δ30 recipients had detectable viremia with a mean peak titer of 1.77 $\log_{10}$ PFU/mL, a mean day of onset of viremia at Day 4.6, a mean day of peak viremia at Day 5.3, and a mean duration of viremia of 3.4 days (Table 8). Fever was not experienced by any participant however, 8/10 rDEN3Δ30 recipients developed a maculopapular rash of which 5 were graded as moderate (ie, Grade 2, defined in the protocol as symptomatic rash [pruritus/pain] that does not interfere with function) in intensity. The mean day of onset of the rash was study Day 7.1 and the mean duration of rash was 21 days. Following a single dose of rDEN3Δ30, 10/10 (100%) of participants seroconverted to DENV-3 with a reciprocal geometric mean peak DENV-3 neutralizing antibody titer of 395.7 (Table 9).

2.3.3.2 *Study CIR 309*

In study CIR309, the protective efficacy of a live attenuated tetravalent dengue vaccine TV005 against challenge with 10^4 PFU of rDEN3Δ30 6 months following vaccination was evaluated in healthy flavivirus-naïve adults. Because the mean peak titer of virus following challenge with rDNE3Δ30 was lower than that achieved with another challenge virus, rDEN2Δ30 given at the same dose [16], a 10-fold higher challenge dose (4 $\log_{10}$ PFU) was chosen in an attempt to increase the peak titer of virus achieved after challenge with rDEN3Δ30. A placebo group was also included. Below, a summary of the data from participants who were challenged with rDEN3Δ30 after having received placebo (N=20) is presented.

Acute dengue illness with fever was not observed in any DEN3Δ30 recipient. All placebo recipients who were challenged with rDEN3Δ30 developed rash. The mean day of onset of the rash was study Day 7.2 and the mean duration of rash was 10.4 days. Seventeen out of 20 (85%) participants developed infectious viremia (detectable by tissue culture). The mean peak titer of rDEN3Δ30 recovered post-challenge was 1.07 $\log_{10}$ PFU/mL (Table 8). The mean day of onset of viremia was at study Day 4.6 and the mean day of peak viremia was at study Day 5.5. The mean duration of viremia was 2 days. Following a single dose of rDEN3Δ30, 17/20 (85%) participants seroconverted to DENV-3 with a reciprocal geometric mean peak DENV-3 neutralizing antibody titer of 333.8 (Table 9). A dose of 4 $\log_{10}$ PFU of rDEN3Δ30 infected only 85% of flavivirus-naïve volunteers.

2.3.3.3 *Study CIR 323*

In study CIR323, the protective efficacy of a live attenuated tetravalent dengue vaccine TV003 against challenge with rDEN3Δ30 or rDEN2Δ30 (ie, a recombinant DENV-2 challenge strain) 28 days following vaccination was evaluated in healthy flavivirus-naïve adults. A placebo group was also included. Below, a summary of the data from participants who were challenged with 3 $\log_{10}$ PFU of rDEN3Δ30 after having received placebo vaccine (N=10) is presented.

rDEN3Δ30 was recovered from all 10 placebo recipients who were challenged with rDEN3Δ30. The mean peak titer of rDEN3Δ30 recovered post-challenge was 1.38 $\log_{10}$ PFU/mL. The mean day of onset of viremia was at Day 5 post-challenge, the mean day of peak viremia was at Day 5.5 post-challenge, and the mean duration of viremia was 3.1 days (Table 8). Nine out of 10 placebo recipients challenged with rDEN3Δ30 developed a rash. The mean day of onset of rash was study Day 8.3 and the mean duration of the rash was 12 days. The rash was graded as moderate in 7 of the 9 placebo recipients who developed rash following challenge. Following a single dose of rDEN3Δ30,

10/10 (100%) of participants seroconverted to DENV-3 with a reciprocal geometric mean peak DENV-3 neutralizing antibody titer of 388.9 (median=618.6), Table 9.

2.3.3.4 *Summary*

rDEN3Δ30, when administered at a dose of 3 log_{10} PFU to flavivirus-naïve participants, induces viremia in 100% of inoculated participants, but is associated with only mild clinical signs and symptoms. The challenge virus does not cause DF but induces rash in 80 to 100% of the participants, and also induces other clinical signs and symptoms consistent with dengue such as headache, retro-orbital pain, and myalgia. A higher dose of the DENV-3 challenge virus (4 log_{10} PFU of rDEN3Δ30) was used in this study to attempt to improve the peak titer post-challenge. Interestingly, when given 3 log_{10} PFU of rDEN3Δ30 in study CIR304 and CIR323, all 20 participants (100%) had rDEN3Δ30 recovered from the blood, had a higher mean peak titer of rDEN3Δ30, and seroconverted to DENV-3, as compared to study CIR309 in which the higher dose of rDEN3Δ30 was able to infect only 85% of the 20 flavivirus-naïve subjects. Based on the viremia and infectivity data from these studies, future challenge studies with rDEN3Δ30 will use a dose of 3 log_{10} PFU as the dose of 4 log_{10} PFU did not result in a higher peak viral load and resulted in fewer subjects seroconverting to DENV-3.

Table 7: Clinical response to rDEN3Δ30 in healthy flavivirus-naïve adults (CIR304, CIR309, and CIR323)

Adverse event	rDEN3Δ30 (n=40)	Control[1] (n=40)	p value (1-sided)[2]
Injection site:			
Erythema	**22.5%**	**0.0%**	**0.0012**
Pain	0.0%	0.0%	n/a
Tenderness	**30.0%**	**0.0%**	**0.0041**
Induration	**15.0%**	**7.5%**	**0.0128**
Systemic:			
Fever	5.0%	0.0%	0.2468
Headache	65.0%	47.5%	0.0880
Rash	**92.5.0%**	**2.5%**	**<0.0001**
Neutropenia[3]	**22.5%**	**2.5%**	**0.0072**
Elevated ALT	0.0%	0.0%	n/a
Myalgia	35.0%	17.5%	0.6031
Arthralgia	12.5%	2.5%	0.1004
Retro-orbital Pain	**45.0%**	**12.5%**	**0.0013**
Fatigue	**45.0%**	**25.0%**	**0.0500**
Prolonged PT	2.5%	7.5%	0.9422
Prolonged PTT	5.0%	0.0%	0.2468
Thrombocytopenia[4]	**12.5%**	**0.0%**	**0.0274**

1. Subjects were their own controls in CIR309 and 323. Four placebo controls were enrolled in CIR304.
2. Probability is greater for rDEN3Δ30 than for placebo
3. Neutropenia was defined as an ANC ≤ 1,000/mm^3.
4. All cases but 1 were mild in intensity. The other case was moderate (≥75,000 - <100,000/mm^3)
5. Bolded values indicated significant p value without multiple comparison's correction
6. n/a = non-applicable

Table 8: Summary of Virologic Response in Flavivirus-naive placebo recipients challenged with rDEN3Δ30

Study	No. Viremic Participants (%)	Dose (log_{10} PFU)	Mean Day of Onset of Viremia	Mean Day of Peak Viremia	Mean Peak Titer (log_{10} PFU/mL)	Mean Duration of Viremia (days)
CIR304 (n=10)	10 (100%)	3	4.6	5.3	1.77	3.4
CIR309 (n=20)	17 (85%)	4	4.6	5.5	1.07	2.0
CIR323 (n=10)	10 (100%)	3	5.0	5.5	1.38	3.1

Table 9: Neutralizing Antibody Response to rDEN3Δ30

	Dose	Geometric mean peak neutralizing antibody titer, reciprocal (median)	% seroconversion
CIR304 (n=10)	3 log_{10} PFU	395.7 (306.5)	100
CIR309 (n=20)	4 log_{10} PFU	333.8 (640)	85
CIR323 (n=10)	3 log_{10} PFU	388.9 (618.6)	100

2.4 Study Products Descriptions

JNJ-64281802 is a novel, potent, pan-serotypic small-molecule inhibitor of dengue virus (DENV) targeting DENV nonstructural protein (NS)4B. JNJ-64281802 is being developed for the prevention and treatment of dengue infection.

The live recombinant virus strain rDEN3Δ30 has been identified as DENV suitable for use in dengue controlled human infection models. This investigational DENV-3 is based on a complementary deoxyribonucleic acid (cDNA)-derived DENV-3 (strain Slemen/78) in which the 3′ UTR of DENV-3 contains a 30-nucleotide deletion (nucleotides 173–143) that is homologous to the Δ30 deletion in the 3′ UTR of rDEN4Δ30 (named Δ30 for consistency) [15].

2.4.1 JNJ-64281802

2.4.1.1 *Clinical Lot Production*

This information will be available for reference in the pharmacy manual.

2.4.1.2 *Final Container of JNJ-64281802*

This information will be available for reference in the pharmacy manual.

2.4.1.3 *Composition of JNJ-64281802*

For Cohort 1, the drug product is supplied as CCI [redacted] For the qualitative composition of the CCI [redacted], please refer to the latest version of the Investigator's Brochure (IB) for JNJ-64281802

For Cohort 2, the drug product is supplied as CCI [redacted] For the

qualitative composition of the CCI refer to the latest version of the Investigator's Brochure (IB) for JNJ-64281802

2.4.1.4 *Investigational Product Label for JNJ-64281802*

The investigational product label for JNJ-64281802 will be provided in the pharmacy manual.

2.4.2 rDEN3Δ30, Lot DEN3#114A

2.4.2.1 *Seed Lot Production*

A plasmid was constructed to encode the entire genome of DENV-3 Sleman/78. The cDNA of the 3′ UTR of the DENV-3 Sleman/78 was then modified to introduce a 31-nucleotide deletion that was homologous to the DEN4Δ30 deletion. Genome-length, capped RNA transcripts were synthesized from the plasmid p3Δ30 and purified. Virus was recovered in qualified Vero cells transfected with purified RNA transcripts using DOTAP liposomal transfection reagent. The virus recovered was designated rDEN3Δ30 and was subsequently terminally diluted three times, and finally passaged an additional two times in Vero cells to generate the seed virus.

2.4.2.2 *Clinical Lot Production*

The rDEN3Δ30 seed virus was transferred from PPD to the PPD as the seed virus for production of the vaccine pool. The virus was amplified by a single passage in Vero cells in serum-free medium to produce the Final Drug Product, rDEN3Δ30 (lot DEN3 #114A). The Final Drug Product was manufactured on July 23, 2014.

2.4.2.3 *Final Container of rDEN3Δ30, Lot DEN3#114A*

The Final Drug Product was dispensed as 0.6-mL aliquots of approximately 6.1 $\log_{10}$ PFU/mL live recombinant dengue virus type 3 rDEN3Δ30 Vero-grown virus vaccine into 1.8-mL sterile cryovials and stored at -80°C ± 15°C. The titer of the rDEN3Δ30 (lot DEN3#114A) Final Drug Product, as determined on August 12, 2014, was approximately 6.1 $\log_{10}$ PFU/mL.

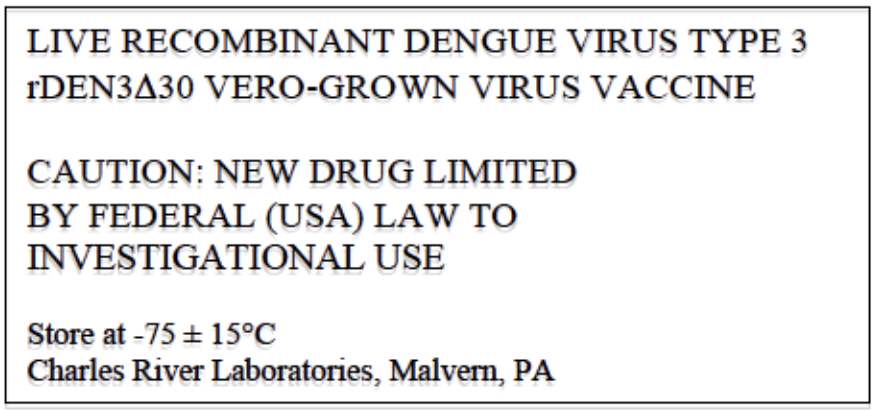
2.4.2.4 *Composition of rDEN3Δ30, Lot DEN3#114A*

The Final Drug Product composition is a concentration of live recombinant rDEN3Δ30 Vero-grown virus vaccine (lot DEN3#114A) in Leibovitz L-15 medium containing 1X sucrose, phosphate buffer, glutamate (SPG).

The potency of rDEN3Δ30 (Lot DEN3#114A) is 6.1 $\log_{10}$ PFU/mL PFU/mL.

2.4.2.5 *Investigational Product Label for rDEN3Δ30, Lot DEN3#114A*

Figure 1: Label for rDEN3Δ30, Lot DEN3#114A (Enlarged Sample)



NOTE: Since manufacture of the Final Drug Product, evaluation of live attenuated DENV vaccines (developed at LID/NIAID/NIH) in both laboratory and clinical situations indicates that these viruses are stable and potent when stored at a temperature of -80°C ± 15°C. Therefore, -80°C ± 15°C is the recommended storage condition for the Final Drug Product.

3 Objectives and Endpoints

3.1 Primary Objectives

1. To assess the antiviral activity of JNJ-64281802 versus placebo in terms of reduction of DENV-3 RNA.

3.2 Secondary Objectives

1. To assess the safety and tolerability of JNJ-64281802.
2. To assess the DENV infection-associated AEs.
3. To assess the antiviral activity of JNJ-64281802 versus placebo on other virologic endpoints.
4. To assess the PK of JNJ-64281802 following repeated oral dosing.
5. To evaluate the relationship between the PK and the antiviral activity of JNJ-64281802.
6. To assess the anti-DENV-3 IgM and IgG antibody responses.

3.3 Exploratory Objectives

1. To determine the rate of uncomplicated dengue infection.
2. To explore the anti-DENV-3 neutralizing antibody response.
3. To explore the anti-DENV-3 cellular immune response.
4. To explore changes in serum protein levels (including cytokines).
5. To explore the DENV-3 NS1 serum protein levels (Cohort 1; optional for Cohort 2).
6. To explore the resistance of DENV-3 to JNJ-64281802.
7. To explore the relationship between the PK and the safety and tolerability of JNJ-64281802.

8. To explore the impact of host and viral baseline factors on the antiviral activity and safety of JNJ-64281802.

3.4 Primary Endpoints

1. Area under the DENV-3 RNA viral load (VL) concentration-time curves from immediately before inoculation (baseline on Day 1) until Day 29 ($AUC_{D1\text{-}D29}$ [VL]).

3.5 Secondary Endpoints

1. Safety and tolerability as measured by recording of AEs, physical examinations, vital signs, ECGs, and clinical laboratory assessments.
2. Occurrence and severity of DENV infection associated AEs.
3. Virologic endpoints derived from quantitative DENV-3 RNA, including:
   - area under the log_{10}-transformed DENV-3 RNA VL concentration-time curves from immediately before inoculation (baseline on Day 1) until Day 29 ($AUC_{D1\text{-}D29}$ [log_{10} VL])
   - peak of detectable DENV-3 RNA
   - duration of detectable DENV-3 RNA
   - time to first onset of detectable DENV-3 RNA
   - presence of detectable DENV-3 RNA
4. Virologic endpoints derived from quantitative peripheral DENV-3 infectious viral titer (further referred to as infectious viremia), including:
   - area under the infectious viremia curves from immediately before inoculation (baseline on Day 1) until Day 29
   - area under the log_{10}-transformed viremia curves
   - peak of detectable viremia level
   - duration of detectable viremia
   - time to first onset of detectable viremia
   - presence of detectable viremia
5. PK (plasma concentrations or exposure parameters) of JNJ-64281802.
6. Occurrence and magnitude of anti-DENV-3 total IgM and IgG antibody titers.
7. Time to first onset of anti-DENV-3 total IgM and IgG antibody titers.

3.6 Exploratory Endpoints

1. Presence of detectable DENV-3 RNA on at least 1 time point during the study with or without DENV infection-associated AEs.
2. Occurrence and magnitude of anti-DENV-3 neutralizing antibody response (optional analysis for Cohort 2).
3. Occurrence and magnitude of anti-DENV-3 cellular immune response.

4. Magnitude of serum proteins (including cytokines).
5. Occurrence and magnitude of DENV-3 NS1 serum protein levels (optional for Cohort 2).
6. Changes in the viral genome sequence (with a focus on NS4B) between virus used for inoculation and virus present during infection in participants with detectable DENV-3 RNA after inoculation.
7. Human leukocyte antigen (HLA) genotyping and pharmacogenomic analyses.
8. Biomarker analysis via transcriptional profiling of host RNA.

3.7 Hypothesis

The primary hypothesis of this study is that the highest dose of JNJ-64281802 is superior to placebo with respect to its antiviral activity in healthy adult participants inoculated with rDEN3Δ30, as measured by DENV-3 RNA VL AUC from immediately before inoculation (baseline on Day 1) until Day 29 ($AUC_{D1\text{-}D29}$ [VL]).

4 Study Design

4.1 Overall Design

This study is a multicenter, randomized, placebo-controlled, double-blind, interventional Phase 2a, study in normal healthy adult subjects 18 – 55 years of age, inclusive, recruited from the metropolitan Baltimore/Washington, DC area & Burlington/Vermont. The study follows an adaptive 2-stage design consisting of 2 cohorts, each with up to 3 groups. The 2 cohorts will be enrolled in a staggered manner. As a safety measure, a sentinel group of 4 participants will be enrolled in Cohort 1 (Group 1a) before enrolling the remaining participants (Group 1b and Group 2) in the cohort.

The purpose of this study is to evaluate the clinical and virologic response to repeated doses of investigation product JNJ-64281802 when administered orally in healthy, DENV and ZIKV-naïve, non-pregnant, adult volunteers who are subsequently inoculated with rDEN3Δ30, a recombinant DENV-3 strain, to explore the antiviral activity of repeated oral doses of JNJ-64281802 versus placebo. The safety, tolerability, PK, and the relationship between the PK and antiviral activity of JNJ-64281802 will also be evaluated. Placebo recipients are included in the study as a control to better assess study agent associated versus non-study agent associated AEs and to act as infectivity controls following administration of rDEN3Δ30.

After providing written informed consent, subjects will undergo eligibility screening, including medical history, physical examination, hematology testing, liver and renal function testing, human immunodeficiency virus (HIV) screening, hepatitis B and C screening, urinalysis, urine toxicology screening, ECG screening, alcohol breath test screening (per PI/provider discretion), COVID-19 testing (if determined necessary by the clinician or per guidelines), and serology screening for previous infection of DENV and ZIKV (Cohort 1) and DENV, ZIKV, West Nile virus, and SLEV (Cohort 2). A two-step approach to screening may be used, as described in section 7.3.

Serum or urine pregnancy testing will be performed on applicable persons of childbearing potential. All screening tests must be performed within 60 days of initiation of JNJ-64281802 study agent at Study Day -5 (Cohort 1) or Study Day -2 (Cohort 2). HIV screening must be performed within 2 weeks of JNJ-64281802 study agent administration. Pregnancy screening will occur at applicable screening visit(s), be repeated on the first day of JNJ-64281802 administration prior to administration, and on

the day of inoculation with rDEN3Δ30 prior to inoculation with rDEN3Δ30. All clinically significant abnormalities will be reviewed with subjects and referral for follow-up care will be provided. Subjects will be determined to be eligible based on the inclusion and exclusion criteria found in section 5 of this protocol. For subjects who are eligible, the Study Day -5 (Cohort 1) or Study Day -2 (Cohort 2) visit will be scheduled for initiation of JNJ-64281802.

For **Cohort 1**: Subjects will present to the inpatient unit on Study Day -6. After eligibility criteria have been reviewed and confirmed, subjects will be admitted during this period of intensive PK sampling. Dosing with JNJ-64281802 or placebo will begin on Study Day -5. Discharge will occur on Study Day -4. Dosing with JNJ-64281802 will be observed in-clinic on Days -5, -4, -1, 1, 3, 5, 7, 9, 11, 14, 16, 18, and 21. Subjects will have phone contact on Days -3, -2, 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, and 20 to record time of dose, time of last food intake, and review AEs and concomitant therapy. Daily dosing with JNJ-64281802 or placebo will occur from Study Day -5 through Study Day 21. On Study Day 21 subjects will present to the unit for a second intensive PK sampling period for a full day. On Study Day 1, all subjects will be challenged with rDEN3Δ30.

For **Cohort 2**: Subjects will present to the inpatient unit on Study Day -3. After eligibility criteria have been reviewed and confirmed, subjects will be admitted during this period of intensive PK sampling. Dosing with JNJ-64281802 or placebo will begin on Study Day -2. Discharge will occur on Study Day 1. Dosing with JNJ-64281802 will be observed in-clinic on Days -2, -1, 1, 4, 6, 8, 11, 13, 15, 18, and 21 for the daily dosing regimen and on Days -2, -1, 1, 8 and 15 for the weekly dosing regimens. In the daily dosing regimen with JNJ-64281802 or placebo, twice daily dosing will occur from Study Day -2 to Study Day -1, and daily dosing from Study Day 1 to Study Day 21. In the weekly dosing regimens, twice daily dosing will occur from Study Day -2 to Study Day -1, and weekly dosing which will occur on Study Day 1, Study Day 8, and Study Day 15. On Study Day 21 for the daily regimen, and on Study Day 15 for the weekly regimens, subjects will present to the unit for a second intensive PK sampling period for a full day. On Study Day 1, all subjects will be challenged with rDEN3Δ30.

During the inpatient visits on Study Day -6 to -4 (Cohort 1) and Study Day -3 to 1 (Cohort 2), the subjects will be evaluated by a clinician and will have blood drawn for clinical laboratory studies, virologic assays, and immunologic assays. During the outpatient visits subjects will return to the clinic for evaluation and for blood draw as specified in the Schedule of Procedures. Study Day 85 will be their final visit. Subjects will have their temperature measured in clinic or measure their temperatures at home twice daily from Study Day 1 through Study Day 29.

4.1.1 Study Design

The study follows an adaptive 2-stage design consisting of 2 cohorts, each with up to 3 groups (Table 10). The 2 cohorts will be enrolled in a staggered manner. As a safety measure, a sentinel group of 4 participants will be enrolled in Cohort 1 (Group 1a) before enrolling the remaining participants (Group 1b and Group 2) in the cohort. Based on the results from Cohort 1, the sponsor (OCRPRO) together with the Drug Development Team (DDT) and DSMB may decide to terminate the study after Cohort 1.

CCI [redacted]. In Cohort 1, a loading dose (LD) period of 5 days will be followed by a maintenance dose (MD) period of 21 days, resulting in a total dosing period of 26 days. Doses will be taken once daily in both the LD and MD periods. The LD will be 3 (high dose regimen) or 4 (medium and low dose regimen) times the

MD. The following doses will be administered in Cohort 1: high dose (600-mg LD for the LD period and 200-mg MD for the MD period), medium dose (200-mg LD for the LD period and 50-mg MD for the MD period), low dose (40-mg dosing LD for the LD period and 10-mg MD for the MD period). Note that the study will not include a "Day 0". CCI [redacted]

In Cohort 2, a loading dose (LD) period of 2 days will be followed by a maintenance dose (MD) that will be administered on one of two schedules: daily for a period of 21 days (group 3) or weekly for a period of 15 days (groups 4 and 5). Doses will be taken twice daily during the loading dose period and once daily during the maintenance dose period for group 3, and once weekly for groups 4, and 5.

The following doses will be administered in Cohort 2:

- Group 3: 800 mg twice daily for LD period (total of 4 doses over 2 days / daily total of 1,600 mg per day for 2 days) and 250 mg daily for MD period (21 days).
- Group 4: 450 mg twice daily for LD period (total of 4 doses over 2 days / daily total of 900 mg per day for 2 days) and 1200 mg weekly for MD period (total of 3 doses administered over 15 days).
- Group 5: 250 mg twice daily for LD period (total of 4 doses over 2 days / daily total of 500 mg per day for 2 days) and 500 mg weekly for MD period (total of 3 doses administered over 15 days).

Table 10: Overview of the Cohorts, Groups, and Number of Participants

Cohort	Group	
Cohort 1[a]	Group 1a (high dose sentinel group): JNJ-64281802 (high dose) (600-mg LD/200-mg MD) versus placebo	N=4 Sentinel Group: 2 high + 2 placebo
	Group 1b (remaining high dose) JNJ-64281802 (high dose) (600-mg LD/200-mg MD) versus placebo	N=12 8 high + 4 placebo
	Group 2 (low/medium dose): JNJ-64281802 (low dose) (40-mg LD/10-mg MD) **AND** JNJ-64281802 (medium dose) (200-mg LD/50-mg MD) versus placebo	N=14 6 low + 6 medium + 2 placebo **Subtotal N: 30[b]**
Cohort 2[c]	Group 3: JNJ-64281802 (800-mg BID LD/250-mg QD MD) versus placebo	8 (6 active + 2 placebo)
	Group 4: JNJ-64281802 (450 mg BID LD/1200 mg Q7D MD) versus placebo	8 (6 active + 2 placebo)
	Group 5: JNJ-64281802 (250-mg BID LD/500-mg Q7D MD) versus placebo	8 (6 active + 2 placebo) **Subtotal N: 24[d]** **Total N: 54**

LD = loading dose; MD = maintenance dose; N = number of participants; BID = 2x daily; QD = daily; Q7D = weekly

CCI [redacted].

[a] A sentinel group of 4 participants will be enrolled before the remaining 26 participants in the cohort. Subjects in Group 1 will be randomized between High dose and placebo. Subjects in Group 2 will be randomized between Low dose, Medium dose, and placebo.

[b] In order to account for a potential early discontinuation, a maximum of 7 participants can be replaced in case of discontinuation before last dose of study drug on Day 21.
[c] The 3 dosing regimens selected for evaluation in Cohort 2 were selected based on interim analysis data from Cohort 1.
[d] In order to account for a potential early discontinuation, a maximum of 6 participants can be replaced in case of discontinuation before Day 21.

The aim of Cohort 1 is to assess CCI the superior antiviral activity of the highest dose of JNJ-64281802 versus placebo and to collect data for the characterization of a relationship between the PK and antiviral activity of JNJ-64281802 based on DENV-3 RNA. In Cohort 2, the aim is to further characterize the relationship between the PK and antiviral activity.

There are 3 sequential phases to the study: screening, dosing (including inoculation with rDEN3Δ30), and follow-up. Participants enrolled in Cohort 1 will attend screening visits between Day -65 and Day -6, inclusive. For these participants, repeated daily oral dosing with JNJ-64281802 or placebo will be initiated on Day -5, a subcutaneous (SC) injection with rDEN3Δ30 will take place on Day 1, and dosing with JNJ-64281802 or placebo will end on Day 21 (ie, a total dosing duration of 26 days). Dosing with JNJ-64281802 will be initiated 5 days before inoculation with rDEN3Δ30 to achieve near-to-steady-state JNJ-64281802 plasma concentrations by the time of inoculation. All participants will be followed up until approximately 64 days after last dose of study drug (ie, Study Day 85).

Participants enrolled in Cohort 2 will attend screening visits between Day -65 and Day -3, inclusive. For these participants, repeated oral dosing with JNJ-64281802 or placebo will be initiated on Day -2, a subcutaneous (SC) injection with rDEN3Δ30 will take place on Day 1, and dosing with JNJ-64281802 or placebo will end on Day 21 (ie, a total dosing duration of 23 days) for the daily dosing group and on Day 15 (ie, a total dosing duration of 17 days) for the weekly dosing groups. Twice daily dosing with JNJ-64281802 will be initiated 2 days before inoculation with rDEN3Δ30 to achieve near-to-steady-state JNJ-64281802 plasma concentrations by the time of inoculation. All participants will be followed until approximately 64 days after last dose of study drug for daily dosing and 70 days after last dose of study drug for weekly dosing (ie, Study Day 85).

Participants will visit the study site at screening visits and at regular time points during the dosing and follow-up phase, as indicated in section 7. Dosing with JNJ-64281802 or placebo, and the SC injection with rDEN3Δ30 will occur in the inpatient and/or outpatient clinical trial unit under the supervision of the study-site personnel. Participants will be kept under observation for at least 30 minutes in the clinical trial unit after initial dosing and/or inoculation to ensure their safety, and any reactions during this period will be documented. This observation period will not be required after Day 1. Participants will stay in-house at the clinical trial unit during the intensive PK sampling period from the morning of Day -6 (Cohort 1) or Study Day -3 (Cohort 2) until at least 24 hours post first dose (ie, the morning of Day -4 [Cohort 1] or Day 1 [Cohort 2]).

Participants will be notified to inform the site of any AE(s). Participants will also be provided with a wallet card to carry with them during the study that provides 24-hour contact information for the study team. A DHCM medical statement to include in the participant's medical file will be provided to the participants or mailed to their primary care physician.

If a participant meets criteria for admission to the inpatient unit (as listed in section 7.18), he or she may be admitted at the investigator's discretion for closer observation.

Key assessments will include the determination of the antiviral activity of JNJ-64281802 versus placebo (measured by DENV-3 RNA and viremia), the safety and tolerability of JNJ-64281802, the PK of JNJ-64281802, and the anti-DENV-3 humoral immune response. Safety and tolerability will be assessed through AE reporting, physical examinations, vital signs, ECGs, and clinical laboratory tests. Furthermore, the effect of JNJ-64281802 on the clinical course of DENV infection will be evaluated based on the investigator's assessment of DENV infection-associated AEs and any DENV infection-associated illness experienced by the participants. In addition, the study will include the collection of blood samples for viral genome sequencing, HLA genotyping and pharmacogenomic (DNA) research, cellular immune response analysis, and exploratory biomarker analyses (including serum protein measurements and transcriptional profiling of host RNA). For more details on all study assessments and procedures, refer to section 7.

For participants who discontinue study drug prematurely for any reason other than withdrawal of consent before the end of the dosing phase, an early dosing withdrawal visit should be scheduled as soon as possible after decision for discontinuation. At the early dosing withdrawal visit, assessments of the Day 21 (Cohort 1 + Cohort 2 daily dosing)/ Day 15 (Cohort 2 weekly dosing) visit will be performed on an outpatient basis, with only the initial PK sample being collected and with the exception of dosing activity. The participants will then enter the 64 or 70-day follow-up phase (depending on daily or weekly dosing regimen), with visits for Day 22-85 (daily dosing) or Day 16-85 (weekly dosing) as indicated in Table 3: Schedule of Procedures – Cohort 1

	Screen[5]		Dosing Study Days (Inpatient visits marked in gray)																									Follow-up Study Days							
lure	-65 to-6	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	25	29	36	43	50	57
on Visit	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
call Visit					X	X			X		X		X		X		X		X	X		X		X		X	X							
ed Consent	X																																		
D-19 screening ns	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
review									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
mid-turbinate wab		[X][10]						[X][10]																				[X][10]							
ght Stay on Unit		X	X																																
Drug Taken			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
-3 Inoculation								X																											
al exam	X[6]		X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
igns	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
ete Medical	X																																		
ion of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
nitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			X					X		X*		X*		X*		X*		X*			X*		X*		X*			X*							
alysis			X[2]	X				X						X		X		X					X					X[13]	X	X	X				X
tative RT-PCR							X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
tive RT-PCR																															X[3]	X	X	X	X
Assay							[X]	[X]		[X]		[X]		[X]		[X]		[X]			[X]		[X]		[X]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
LISA							X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
IgM ELISA			X					X										X			X		X		X			X	X	X	X	X	X		X
lizing Antibody								X										X							X			X			X				
Protein Analysis			X							X						X					X				X								X		
Genome cing														[X]		[X]		[X]			[X]		[X]		[X]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
isolation			X													X							X								X				
NA Analysis			X							X						X					X				X								X		

	Screen[5]		Dosing Study Days (Inpatient visits marked in gray)																								Follow-up Study Days							
lure	-65 to-6	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	25	29	36	43	50	57
Genotyping & acogenomics			X																																
																		X							X						X				X
stry Panel[9]	X		X				X					X																	X						
ith differential	X		X				X					X						X							X				X		X				X
T	X		X				X					X						X							X				X		X				X
CV, HBV	X																																		
Zikv screening	X																																		
ncy Test[1]	X		X					X																				X			X				
est[11]	X																																		
ysis & Urine ogy Screen	X																																		
l Breath Test		X[14]																																	
l ECG[8]	X		X					X																				X							

Aes = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PT/PTT = prothrombin time/partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction

15. Serum or urine pregnancy testing only performed for persons of childbearing potential..
16. On SD -5: 7 PK samples will be collected during 16-hour window.
17. Qualitative RT-PCR will be performed on samples collected on **Days 29, 36, 43, 50, 57, 63, 70, and 85.** If the participant is DENV-3 positive detected for first time at Day ≥29, qualitative RT-PCR will be performed **twice weekly (preferably with 3 to 4 days in between samples)** until the participant results are negative and until resolution of DENV infection-associated Aes. Participants who are DENV-3 positive on Day 85 should return for additional clinical and virologic assessments until the participant results are negative and until resolution of DENV infection-associated Aes. Additional testing using different nucleic acid based methods for the detection and/or quantification of DENV-3 may be performed.
18. Phone calls to collect time of dose, time of last food, AE's, and concomitant therapy on SD -3, -2, 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, and 20.
19. Screening may occur over multiple visits. Certain procedures must be performed within different time frame relative to dosing, see Section 7.1. Screening window is Day -65 to Day -6.
20. A complete physical exam will be performed at screening and on Day 85. At all other indicated timepoints a focused physical exam will be performed.
21. [X] Sample will be collected, but test will only be performed if indicated by guidelines in the protocol.
22. **ECGs are recorded pre-dose on dosing days.**
23. Chemistry panel consists of sodium, potassium, chloride, bicarbonate, BUN, calcium, phosphate, albumin, total protein, total cholesterol, creatinine, glucose, AST, ALT, GGT, HDL cholesterol, LDL cholesterol, triglycerides, magnesium, calculated creatine clearance (by MDRD), lipase, amylase, total bilirubin, alkaline phosphatase, uric acid
24. Nasopharyngeal (NP) or mid-turbinate swab to test for SARS-CoV 2 – the virus that causes COVID-19 – will be collected from all volunteers regardless of vaccination status based on guidance from federal, state, local, and/or institutional health officials* or at the discretion of the clinician (may be collected up to 72 hours in advance of stated collection time).
    *This guidance may be informed by the local COVID infection rate, severity of infections, vaccination rates, and other factors as the COVID-19 pandemic continues to evolve and change. NP or mid-turbinate swabs may be collected at other time-points if volunteer has COVID-like symptoms.
25. FSH performed only in females who have stopped menstruating for > 12 consecutive months but < 24 months. (Anyone who has had amenorrhea > 24 consecutive months is considered postmenopausal and does not require FSH).
26. In participants who develop a rash, an additional sample will be collected at onset of rash and tested. Noted on this chart with an asterisk {X*}
27. On Study Day 21: 6 PK samples will be collected during a 12-hour window
28. Alcohol breath test may be performed at the discretion of PI/provider upon admission to inpatient unit

(Cohort 1) and Table 4 (Cohort 2).

A DDT as well as the NIAID Intramural Data and Safety Monitoring Board (DSMB) and Drug Development Unblinded Team (DDUT) will be commissioned for this study.

The DDT is the Janssen core study team in charge of the development of the Janssen investigational product JNJ-64281802 and includes, but is not limited to, the Compound Development Team Leader, the Medical Lead, the PK Lead, the Biostatistician, and the Virologist. The primary responsibilities of this team are to review the blinded safety data report generated by the DSMB from the sentinel group in order to determine if the safety and tolerability of the dosing with JNJ-64281802/placebo and inoculation with rDEN3Δ30 were shown to be acceptable to allow dosing of the remainder volunteers of Cohort 1; to review the unblinded pharmacokinetic and virologic data at the interim analysis after Cohort 1 Group 1 reached Day 29 CCI to review the unblinded pharmacokinetic and virologic data at the interim analysis after Cohort 1 (Groups 1a, 1b, and Group 2) complete Day 85 in order to determine the dosing strength and periodicity of JNJ-64281802 for Cohort 2 of the study; to review all available safety data if one of the study pausing rules have been met, in order to determine the next steps. The DDT will submit the written DDT summary reports with recommendations to the DSMB.

The NIAID Intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The NIAID Intramural DSMB is constituted to review the safety data of Intramural NIAID clinical studies that require DSMB oversight, and consists of experts in infectious diseases, biostatistics, and clinical trials. The Principal Investigator (PI)/designee will provide the DSMB executive secretary with blinding codes in a sealed envelope in case the DSMB requires this information to make its recommendations. The DSMB will review the study prior to initiation and twice a year thereafter and will be involved in the unblinded evaluation of the data of the first 4 participants in Cohort 1 and in the interim analysis of all participants in Cohort 1 (section 9.6.8). The DSMB will make recommendations regarding continuation or discontinuation of the study at these times. These reviews may or may not include unblinded data. The Board may convene additional reviews as necessary. Prior to each review, a summary of cumulative safety data will be submitted in a format acceptable to the Board together with the DDT and/or DDUT reports if available. The Board will review the study data to evaluate the safety, efficacy, study progress and conduct of the study. Reports of SAEs and deaths will be submitted by the PI to the Board at the same time they are reported to the sponsor and IRB. All Unanticipated Problems (UPs) will be submitted to the DSMB at the same time they are submitted to the IRB or IND sponsor. IND Safety Reports will be submitted to the DSMB by the investigator after their receipt. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI will notify the Board when specific pausing rules are met (section 8.5) and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB(s).

The DDUT will consist of Janssen personnel, namely a clinician with expertise in infectious diseases, a virologist, a medical safety officer, a pharmacometrician, and a statistician, none of whom will be part of the DDT. If, in the judgment of the investigator and/or the Sponsor (OCRPRO) medical monitor, a significant or unexpected safety event occurs, the DSMB will decide if a review of unblinded safety data will be needed. The DSMB will formulate recommended decisions/actions to the DDUT with respect to any changes to conduct that is deemed necessary based on the emerging safety and tolerability data. This may include the pause or closure of treatment arms. The final decision will be taken in collaboration between the DSMB and the DDUT. The DDUT will also be involved in

the first interim analysis after Group 1a and Group 1b (high dose) and in the second interim analysis of all participants in Cohort 1 during which the DSMB, study team, DDT and DDUT will be unblinded (section 9.6.8). The DDUT will also be involved in the unblinded first interim analysis after Group 1a and Group 1b (high dose) completed Day 29 and in the unblinded second interim analysis when all participants in Cohort 1 completed the Day 85 (

Table 11: Summary of Schedule of Interim Analyses and Unblinding of Data

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The independent internal pharmacometrician of Janssen may receive unblinded treatment assignments prior to completion of Study Day 85 of Cohort 1, Group 2 with adequate firewalls so the DDT will remain blinded. This earlier unblinding of the pharmacometrician can be done in order to allow the preparation of the PK/PD model needed to assess the objective of the PK/PD relationship after the second interim analysis.

Table 11: Summary of Schedule of Interim Analyses and Unblinding of Data

	Blinded or unblinded	Reviewed by	Timeline
Sentinel Review Cohort 1, Group 1a (n=4)	Unblinded	DSMB only	After sentinel group (Group 1a) completes D21
CCI Interim Analysis #1: Cohort 1, Group 1b (n=12) Cohort 1 Group 1	Unblinded	DSMB, DDUT[1], DDT	After Group 1a and 1b completes D29
		Study Team	After Group 1a and 1b completes D85
Interim Analysis #2: Cohort 1, Group 2 (n=14)	Unblinded	DSMB, DDUT[2], DDT, and Study Team	After Group 2 completes D85

1. The DDUT may request one or more subjects' treatment assignment prior to study day 29 for review of a safety issue only.
2. The DDUT may request one or more subjects' treatment assignment prior to study day 85 for review of a safety issue only.

4.1.1.1 *Initial Enrollment of Sentinel Cohort 1*

The first 4 participants in Cohort 1 (Group 1a) will receive the first dose of study drug or placebo at least 21 days before the remaining 26 participants in the cohort. These 4 participants will first be randomized in a 1:1 ratio to the high-dose group or placebo (Group 1a).

4.1.1.2 *Enrollment of Remaining Subjects in Cohort 1*

The remaining 12 participants in Group 1b will be randomized in a 2:1 ratio to the high-dose group or placebo. Participants in Group 2 will be randomized in a 3:3:1 ratio to the low dose of JNJ-64281802, medium dose of JNJ-64281802, or placebo (Table 10). The LD will be 3 times (high dose regimen) or 4 times (medium and low dose regimen) the MD. CCI [redacted] The following LD/MD regimens will be selected for the 2 groups in Cohort 1:

- High-dose regimen; 600-mg LD (Days -5 to -1)/200-mg MD (Days 1 to 21).
- Medium-dose regimen; 200-mg LD (Days -5 to -1)/50-mg MD (Days 1 to 21).
- Low-dose regimen; 40-mg LD (Days -5 to -1)/10-mg MD (Days 1 to 21).

CCI [redacted]

CCI [redacted]

A first interim analysis will be performed when all participants from Group 1a and Group 1b have completed the Day 29 visit or discontinued earlier CCI [redacted]. Enrollment will not be stopped during this interim analysis. This interim analysis will include PK analysis, DENV RNA analysis, and safety analysis. A second interim analysis will be performed when all participants from Group 1 and Group 2 have completed the Day 85 visit or discontinued earlier. This analysis will be done to select the dose regimens for Cohort 2.

4.1.1.3 *Enrollment of Subjects in Cohort 2*

Based on the interim analysis results of Cohort 1, three separate dosing regimens were selected for Cohort 2 (Table 10).

Within Cohort 2, randomization will be balanced over the different groups by using randomly permuted blocks. Randomization within blocks will be 1:1:1:1 with 1 participant assigned to each of the 3 JNJ-64281802 dose regimens and the last participant of each block assigned to 1 of the 3 corresponding placebo regimens. The 3 placebo regimens will be equally balanced over the different blocks. The dosing duration will not exceed the maximum dosing duration (31 days) of study 64281802DNG1001. Selected dose regimens and rationales are below:

- Group 3: 800 mg twice daily for LD period (total of 4 doses over 2 days / daily total of 1,600 mg per day for 2 days) and 250 mg daily for MD period (21 days). The rationale being to maximize JNJ-64281802 antiviral activity for daily dosing within NOAEL safety limits.

- Group 4: 450 mg twice daily for LD period (total of 4 doses over 2 days / daily total of 900 mg per day for 2 days) and 1200 mg weekly for MD period (total of 3 doses administered over 15 days, ie, Day 1, 8, and 15). The rationale being to maximize JNJ-64281802 antiviral activity for weekly dosing within NOAEL safety limits.

- Group 5: 250 mg twice daily for LD period (total of 4 doses over 2 days / daily total of 500 mg per day for 2 days) and 500 mg weekly for MD period (total of 3 doses administered over 15 days, ie, Day 1, 8, and 15). The rationale being to further characterize the PK/PD relationship of JNJ-64281802.

CCI [redacted]

4.1.2 Sample Size and Placebo Ratio

The target sample size is 54 male and female adult participants, 18 to 55 years of age, who receive rDEN3Δ30 on Day 1 and complete the JNJ-64281802 dosing period. The total sample size for the study will be a maximum of 67 individuals over the 2 cohorts, including a maximum of 7 participants in Cohort 1 and 6 participants in Cohort 2 who can be replaced in case of discontinuation before Day 21. Any subject who does not receive study agent due to ineligibility or withdrawal of consent prior to administration of JNJ-64281802 will not be considered enrolled and therefore will not be followed.

4.1.3 Duration of Subject Participation

Subjects will be followed for approximately 90 days. Subjects will be screened up to 60 days prior to initiation of JNJ-64281802 on Study Day -5 (Cohort 1) or Study Day -2 (Cohort 2). The total duration of study participation (including screening) will be approximately 91 to 150 days.

4.1.4 Estimated Duration of the Study

The entire duration of the study is approximately 99 weeks. Screening procedures should be completed within 60 days prior to initiation of the test article JNJ-64281802. The study will last for approximately 90 days from the time the last subject initiates JNJ-64281802.

4.1.5 Treatment Assignment

Subjects will be randomly assigned to receive JNJ-64281802 or placebo. Treatment assignment will be determined using a random number generator to prepare the sequence in which subjects are assigned to receive JNJ-64281802 or placebo, and all subjects will receive DENV-3 challenge. The randomization will be balanced by using randomly permuted blocks and will be stratified by center. If a group is recruited over different centers, each center should recruit complete blocks (Table 10). A master log of treatment assignments will be maintained in a separate record from other study Records, in a locked room with limited access. A sealed envelope containing a copy of the treatment assignment will also be kept by the DSMB executive secretary.

Subjects will not be informed of their treatment assignment unless requested in writing. If a subject requests to be informed of their treatment assignment, they may be notified of this after the last subject in their Group (Cohort 1, Group 1 or Group 2) or Cohort 2 completes Study Day 85 and the dataset for that group/cohort is cleaned and closed, as notifying them early may unblind study staff.

4.1.6 Blinding

This study will be conducted as a double-blind study to avoid biased assessment of AEs. Different CCI strengths will be used for the different dose levels that will be administered (Table 10)/different (daily-weekly) regimen (Cohort 2). As CCI the dose levels/regimens are different in appearance, blinding across the groups cannot be achieved. However, the dose selection in Cohort 1 will permit the blind to be maintained between the 2 lowest dose groups. To enable blinding within groups, matching placebo CCI for each dose level/regimen will be provided. The study will be unblinded according to treatment cohort and group to enable a better understanding of the safety profile of the drug. Cohort 1, Group 1 will be unblinded for the DDT after participants in Group 1 complete Study Day 29 and the database has been cleaned and closed. The Study Team will be unblinded after participants in Group 1 complete Study Day 85. Cohort 1, Group 2 will be unblinded after participants in Group 2 complete Study Day 85 and the database has been cleaned and closed. Cohort 2 will be unblinded after participants in Cohort 2 complete Study Day 85 and the database has been cleaned and closed.

The subject, investigator, and clinical staff will not know which treatment group the subject has been assigned until the specified timepoint. In addition, other personnel assigned to monitor the study will not know the treatment assignment of the subject. The pharmacist will be unblinded as the study drug will be provided in HDPE bottles. To allow selection of samples, the bioanalytical laboratory will receive randomization lists per treatment. Unblinding of the randomization code will be performed at the bioanalytical laboratory only and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the conduct of the study. No one outside of the lab will have access to this information until the study is unblinded as described above. Randomization codes will be disclosed fully only if the study timepoints described have been met and the clinical database related

to the enrollment group is cleaned and closed. However, the randomization codes and the translation of randomization codes into study drug groups will be disclosed for the interim analyses as described in section 9.6.8. Codes will only be disclosed for subjects included in the analyses. And if it becomes necessary to unblind a specific subject's assignment for emergency medical management, the PI will contact the Investigational Drug Service research pharmacy unblinded study staff and obtain the treatment assignment of the subject in question. Only that specific subject's treatment assignment will be unblinded. The DSMB will receive the treatment assignment, if the Board felt it necessary. Janssen would not receive the unblinded treatment assignment in this case.

5 Selection and Enrollment of Subjects

Screening for eligible participants will be performed during screening visits between Day -65 (Cohort 1) or Day -62 (Cohort 2) and Day -6 (Cohort 1) or Day -3 (Cohort 2). In case the first screening visit is planned to take place within 14 days before first dose of study drug, additional screening visits may not be applicable, and all screening assessments may be performed during one single screening visit. If there are multiple screening visits, some assessments may be repeated. An inclusion/exclusion criteria check is performed at screening and before administration of the first dose of study drug on Study Day -5 (Cohort 1) or Study Day -2 (Cohort 2). Additionally, participants will be evaluated prior to challenge administration on Study Day 1 to ensure that they do not meet any criteria which would exclude them from rDEN3Δ30 challenge.

Note: The screening period between the first screening visit and the first dose of study drug may be prolonged beyond 60 days for a participant following a case-by-case evaluation and discussion with the DDT.

The inclusion and exclusion criteria for receipt of JNJ-64281802 test article and for receipt of rDEN3Δ30 challenge are described below. If there is a question about these criteria, the investigator must consult with the drug development team and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to section 9.1, Sample Size Determination.

5.1 Inclusion Criteria for Receipt of JNJ-64281802 Test Article

Each potential participant must satisfy all of the following criteria to receive the JNJ-64281802 test article:

1. Male or female.
2. 18 to 55 years of age, inclusive, at time of screening.
3. Healthy on the basis of physical examination, medical history, and vital signs performed at screening. If there are abnormalities, the participant may be included only if the investigator judges the abnormalities to be not clinically relevant. This determination must be recorded in the participant's source documents.
4. Healthy on the basis of clinical laboratory tests performed at screening. Abnormalities in laboratory tests will be graded according to the modified US FDA Toxicity Grading Scale (section 13.1). Participants with laboratory abnormalities of Grade 1, except AST/ALT tests, may be included only if the investigator judges the abnormalities or deviations from normal to

be not clinically relevant. Assessment of renal toxicity will be made using the creatinine value and not the eGFR in the toxicity table.

5. Must pass the comprehension assessment indicating that the participant understands the purpose, procedures, and potential risks and benefits of the study, after reading the informed consent and after the investigator or designee has provided detailed information on the study and answered the potential participant's questions.

6. Must have a body mass index (BMI, weight in kg divided by the square of height in meters) between 18.0 and 35.0 kg/m^2, extremes included.

7. Must have a normal 12-lead ECG at screening (machine read and/or assessed by investigator or cardiologist), including normal sinus rhythm (heart rate between 45 and 100 beats per minute [bpm], extremes included), QTcF [17] ≤450 ms for male participants and ≤470 ms for female participants, QRS interval <110 ms, and PR interval ≤220 ms. If the results of the ECG are outside the normal ranges, the participant may be included only if the investigator judges the deviations from normal to be not clinically relevant. This determination must be recorded in the participant's source documents and initialed and dated by the investigator.

8. Must have a blood pressure (after the participant is supine for ≥5 minutes) between 90 and 140 mmHg systolic, extremes included, and ≤90 mmHg diastolic at screening. Two repeat measurements are allowed in the absence of any other concerning health screening issues.

9. Must complete the informed consent process independently and without assistance and sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

10. All persons of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin) pregnancy test at screening.

11. A volunteer must be (as defined in section 13.2, Appendix 2: Contraceptive and Barrier Guidance)

    a. Not of childbearing potential, or

    b. Of childbearing potential and practicing a highly effective, preferably user independent method of contraception and agrees to remain on a highly effective method while receiving study drug and until 90 days after the last dose - the end of relevant systemic exposure.

    c. **Note**: The interaction between JNJ-64281802 and hormone-based contraceptives has not been assessed. The efficacy of hormone-based contraceptives may be decreased when co-administered with JNJ-64281802 and therefore a person of childbearing potential using hormone-based contraceptives must use an additional, barrier-based contraceptive method.

12. A person of childbearing potential must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 90 days after the last dose of study drug.

13. During the study and for 90 days after the last dose of study drug, persons who are having sexual relationships in which their partner may become pregnant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Persons who are

having sexual relationships in which their partner may become pregnant should also be advised of the benefit for their partner to use a highly effective method of contraception as condoms may break or leak.

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

15. Must be willing and able to adhere to the study requirements and lifestyle restrictions specified in the protocol. See section 5.1.1, below for details on lifestyle considerations.

16. Available for the duration of the study, which is approximately 85 days after challenge.

Note: Retesting of abnormal values that may lead to exclusion will be allowed per PI's discretion. Retesting to replace lost samples or broken tubes is permitted. Retesting will be performed during an unscheduled visit within the screening phase (within 60 or 14 days before first dose of study drug, as appropriate). Participants with a normal or non-clinically significant value (≤ Grade 1, except for ALT/AST) at retest may be included.

5.1.1 Lifestyle Considerations for JNJ-64281802

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

1. Refer to section 7.21, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

3. Unusual strenuous exercise may affect study-specified assessments and safety laboratory results; for this reason, unusual strenuous exercise (as assessed by the investigator) should be avoided from ≥4 days before first dose of study drug (Day -9) until 30 days after last dose of study drug (Day 51).

4. Must not donate blood or blood products during the study or within 6 months after last dose of study drug.

5. Must not participate in another investigational study with the exception of a COVID 19 vaccine study during the study or within 90 days after last dose of study drug.

6. Must not travel to any dengue-endemic region (as defined by the United States Centers for Disease Control and Prevention [CDC] [18]).

7. Must limit the use of food or drinks/beverages containing alcohol to the absolute minimum from 1 day (Cohort 1) or 48 hours (Cohort 2) before first dose of study drug (Day -6 for Cohort 1 and Day -4 for Cohort 2) until Day 85.

    a. It is recommended to not use alcohol from screening until the Study Day 25 follow-up visit.

   b. However, if any alcohol is consumed, up to 2 standard drink consumptions daily will be allowed. A standard drink is defined as a 350 mL glass of 5% alcohol-by-volume (ABV) beer, a 150 mL glass of 12% ABV wine, or a 45 mL glass of 40% ABV (80 proof) spirit.

8. Must refrain from consumption of grapefruit or grapefruit juice from 7 days before first dose of study drug (Day -12 [Cohort 1] and Day -9 [Cohort 2]) until Day 85.

9. Must refrain from all use of energy drinks and avoid excessive use of caffeine from 48 hours before first dose of study drug (morning of Day -7 for Cohort 1 and Day -4 for Cohort 2) until Day 85.

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

10. May not use drugs of abuse (including amphetamine, barbiturate, cocaine, methadone, and opiates) until 3 weeks after the last dose of study drug.

11. Should not consume any food containing poppy seeds or codeine-containing formulation starting 72 hours before the screening visits and before any visit during the follow-up phase (to avoid a false-positive urine drug test).

12. Cohort 1: Should follow the restrictions on food and water intake and the instructions for the timing of the standardized meals provided during intensive PK sampling (refer to Table 3).

    Cohort 2: The study intervention is to be taken in fed conditions, ie, within 30 minutes after the start of the participant's regular meal or snack, as applicable. During onsite visits up to Day 21 a standardized meal will be provided a maximum of 30 minutes prior to dosing. The time of the meal will be recorded in the eCRF.

5.2 Exclusion Criteria for Receipt of JNJ-64281802 Test Article

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

1. History of liver or renal impairment (creatinine normal ranges; significant cardiac, vascular, pulmonary, gastrointestinal (such as significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability [eg, constipation lasting >2 days]), endocrine, neurologic, hematologic, rheumatologic, neoplastic, autoimmune, or metabolic disturbances.

2. Known allergies, hypersensitivity, or intolerance to JNJ-64281802 or its excipients (refer to the IB for JNJ-64281802), or anaphylaxis or angioedema following JNJ-64281802 administration.

3. History of a severe allergic reaction or anaphylaxis.

4. Taken any disallowed therapies as noted in section 7.21, Concomitant Therapy before first dose of study drug.

5. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 6 months before first dose of study drug, or is currently enrolled in an investigational study, or is planning to be enrolled in an investigational study within 90 days after last dose of study drug. With the exception of participation in COVID-19 vaccine trials and/or receipt of COVID-19 vaccines licensed or under Emergency Use Authorization (EUA) which can be received at any time.

6. Persons of childbearing potential only: Pregnant as determined by a positive β-human chorionic gonadotropin test, breastfeeding, or planning to become pregnant during the study or within 90 days after last dose of study drug.

7. Plans to impregnate and help conceive a child during the study or within 90 days after last dose of study drug.

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

9. Blood test confirming current infection with human immunodeficiency virus type 1 or 2 (HIV-1 or HIV-2), hepatitis B virus (HBV), or hepatitis C virus (HCV).

10. Cohort 1: Blood test confirming past or current infection with or vaccination for any of the following flaviviruses: DENV or Zika virus (ZIKV).

    Cohort 2: Blood test confirming past or current infection with any of the following flaviviruses: DENV, Zika virus (ZIKV), West Nile virus, or SLE virus or history of vaccination (licensed or experimental) for dengue, Zika virus, or Japanese Encephalitis virus (JEV).

    Note: Blood laboratory testing will assess the presence of antibodies at screening.

11. Recent (in the past 4 weeks) travel to any dengue-endemic region (as defined by the US CDC) or having definite plans to travel to a dengue endemic region during the study. Potential participants may be eligible for enrollment ≥4 weeks after their return from a dengue-endemic region.

12. Received or plans to receive:

    d. Licensed live attenuated vaccines - within 28 days before first dose of study drug until 28 days after last dose of study drug.

    e. Other licensed (not live) vaccines - within 14 days before first dose of study drug until 14 days after last dose of study drug.

    f. COVID-19 vaccines, either licensed or under EUA, are allowed at any time during the study however every effort will be made to avoid the above windows of time of administration.

    Note: Vaccinations against DENV and Zika virus are not allowed until 90 days after last dose of study drug.

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

14. Any clinically relevant skin disease (as assessed by the investigator) in the past 6 months, such as active dermatitis, active eczema, drug rash, psoriasis, , and urticaria.

15. Having donated or lost >1 unit of blood (500 mL) within 30 days or >1 unit of plasma (250 mL) within 7 days before first dose of study drug or having the intention to donate blood or blood products during the study and within 6 months after last dose of study drug.

16. Receipt of blood products within the past 6 months of initiation of study drug, including transfusions or immunoglobulin, or anticipated receipt of any blood products or immunoglobulin during the 28 days following challenge.

17. Known or suspected congenital or acquired immunodeficiency or use of immunosuppressive corticosteroids (excluding topical and nasal) or immunosuppressive drugs within 28 days before first dose of study drug until 28 days following the last dose of study drug.

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

18. Use of any strong cytochrome P450 (CYP) 3A4 inhibitors (eg, clarithromycin, itraconazole), CYP3A4 inducers (eg, phenytoin, rifampin), or substrates for CYP3A4 with a narrow therapeutic range (eg, alfentanil, cyclosporin), UGT1A9 inhibitors or inducers (eg, probenecid, rifampin, mefenamic acid), CYP2C8 (eg, repaglinide), CYP2C9 (eg, warfarin, tolbutamide), BCRP (eg pravastatin, folic acid), or CYP2C19 (eg, S-mephenytoin, omeprazole) within 14 days before first dose of study drug. Certain other medications are allowed including metformin, levothyroxine, H_1 and H_2 receptor antagonists, weak CYP3A4 inhibitors, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic anti-depressants, anxiolytics, and benzodiazepines.

19. Any significant alcohol or drug abuse in the past 12 months that has caused medical, occupational, or family problems, as indicated by participant history, or positive test result(s) for drugs of abuse (including amphetamine, barbiturate, benzodiazepine, cocaine, methadone, and opiates) at screening.

20. Behavioral, cognitive, or psychiatric disease that, in the opinion of the investigator, affects the subject's ability to understand and cooperate with the requirements of the study protocol.

21. Severe asthma (emergency room visit or hospitalization within the last 6 months).

22. Asplenia.

23. Refusal to allow specimen storage for future research.

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

NOTE: The investigator should ensure that all study enrollment criteria have been met at screening. All available clinical laboratory results and any other assessments performed in between the screening visits and first dose of study drug should be taken into consideration before enrollment. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before first dose of study drug such that he or she no longer meets all eligibility criteria, then the participant should not be randomized and should not enter the dosing phase.

5.3 Exclusion Criteria for rDEN3Δ30 Challenge

Participants meeting any of the following criteria at the planned time of inoculation with rDEN3Δ30 Challenge will not be eligible for the inoculation and will be withdrawn from the study or changed to off treatment and followed for safety, based on the investigator's discretion:

1. Body temperature ≥38.0°C (100.4°F), confirmed by repeat measurements at least 10 minutes after the first measurement.

2. Acute illness.

3. Any other clinical or laboratory finding that would exclude the participant from inoculation (including, but limited to, a positive urine/serum pregnancy test), as assessed by the investigator.

5.4 Early Discontinuation of Study Drug

For participants who discontinue study drug prematurely for reasons other than withdrawal of consent, an early discontinuation of study drug visit should be scheduled as soon as possible after decision for discontinuation. During the early discontinuation of study drug, assessments of the Day 15 (Cohort 2 only)/21 visit should be performed with only the initial PK sample to be drawn and with the exception of dosing activity. The participants will then enter the 64-day follow-up phase.

5.5 Subject Withdrawal and Termination Criteria

A subject will not be considered to have completed the trial if any of the following apply. However, any subject who has received JNJ-64281802, rDEN3Δ30, or placebo, will be encouraged to remain in the study at the discretion of the investigator and follow the guidelines in section 5.4 or at the discretion of the investigator. Up to 7 participants in Cohort 1 and 6 participants in Cohort 2 may be replaced if subjects are withdrawn prior to Study Day 21.

1. **Research terminated by Sponsor, DDT, or Investigator** – applies if the entire study is terminated by the sponsor, DDT, or investigator for any reason.

2. **Withdrawal of consent** – applies to a subject who withdraws consent to participate in the study for any reason.

3. **Noncompliant with protocol** – applies to a subject who does not or is not able to comply with protocol-specific visits or evaluations on a consistent basis such that adequate follow-up is not possible, and the subject's safety and integrity of the study data would be compromised by continuing in the trial.

4. **Withdrawn by PI** – may occur if the investigator believes that it is in the best interest of the subject to be withdrawn from the study.

5. **Other** – is a category used when previous categories do not apply and requires an explanation.

5.6 Special Situations:

5.6.1 Corrected QT (QTc) Prolongation

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This will be documented appropriately in the source documentation. Any new clinically relevant finding should be reported as an AE. A participant who meets either of the following criterion based on the ECG readings will be withdrawn from study intervention but will continue to be followed for safety.

- QTc >500 msec
- Change from baseline of QTc >60 msec

5.6.2 Pregnancy

Any subject who becomes pregnant during the study period will be encouraged to remain in the study for periodic safety evaluations and will be followed until completion of her pregnancy and one additional visit as needed to obtain pregnancy outcome information. The subject will be asked to sign a release of medical information form so that records can be obtained from her obstetrician regarding the outcome of the pregnancy.

5.6.3 Lost to Follow Up

A subject who is not reachable by telephone or other means of communication and therefore not able to be located is considered lost to follow-up. A subject may be considered lost to follow-up and withdrawn from the study once 3 documented attempts have been made to contact the subject, followed by nonresponse to a certified letter to the last known address requesting that the subject contact the clinical site.

5.6.4 Incarceration

In the event a subject becomes incarcerated during the study, he or she will be taken off treatment for the duration of his/her incarceration. He/she may be terminated from the study if the period of incarceration will prevent the subject from making the scheduled visits.

5.6.5 Missed dose(s)

- Participants that miss 1 dose during the Loading Dose Period (Day -5 to Day -1 for Cohort 1, and Day -2 to Day -1 for Cohort 2) will need to stop the study treatment and be replaced. The new participant will be assigned to the same treatment as the withdrawn subject that they replace.
- Participants, with the exception of weekly dosing in Cohort 2, that miss 2 consecutive doses during the Maintenance Period (Day 1 to Day 21) will need to stop the study treatment and be replaced. The new participant will be assigned to the same treatment as the withdrawn subject that they replace.
- For participants, with the exception of weekly dosing in Cohort 2, that miss 2 doses in one week during the Maintenance Period (Day 1 to Day 21), the site needs to contact the Janssen Clinical Research Manager and the sponsor immediately and the Janssen study team will decide on a case-by-case basis whether the subject needs to be replaced or can continue.
- Participants receiving weekly dosing in Cohort 2 that miss a dose during the Maintenance Period (Day 1 to Day 15) will need to stop the study treatment and be replaced. The new participant will be assigned to the same treatment as the withdrawn subject that they replace.

For information on the dosing windows, please refer to the pharmacy manual.

5.7 Access to Medical Records

The medical history of a subject will be obtained from the subject and will be documented. Medical records from an outside institution may be requested to verify method of contraception and may also be requested to clarify the subject's medical history or clarification of AEs as needed. Medical records from an outside institution will not be requested without the medical release form signed by the subject.

6 Study Product Preparation

6.1 JNJ-64281802 Pre-dosing Preparation

JNJ-64281802 is being developed by Global Public Health, a division of Janssen Pharmaceutica NV., represented by Janssen Pharmaceutica NV in Belgium and by Janssen Research and Development, LLC in the United States.

All JNJ-64281802 CCI must be stored at controlled temperatures as indicated on the product-specific labeling. Any temperature excursion must be reported to the drug development team within one business day of knowledge of the excursion. After exposure to a temperature excursion, the CCI will not be used until written approval has been given by the drug development team.

On Study Day -1 (Cohort 1) or Study Day 1 (Cohort 2), study site personnel will instruct participants of group 3 (participants assigned to daily dosing) on how to store study drug for at home use.

Refer to the pharmacy manual/study -site investigational product and procedures manual for additional guidance on JNJ-64281802 handling and storage.

6.2 Pre-Inoculation Preparation

Monovalent challenge virus for this protocol will be stored at a NIAID-contracted repository until requested by the clinical site. Vials of frozen test agent for administration will be formally requested for transfer to the clinical site by the PI/designee after Institutional Review Board (IRB) approval for the study has been granted and the Food and Drug Administration (FDA) has been in receipt of the protocol for at least 30 days without issuing a clinical hold. The test agent may be transferred to the study site prior to IRB approval and FDA review only for the purpose of determining the titer of the test agent.

After transfer to the clinical site, monovalent virus will be stored in a locked freezer at -80°C ± 15°C until time of use. Each virus is supplied as a concentrate that must be diluted with PlasmaLyte A Injection pH 7.4. to the proper dose prior to administration. PlasmaLyte is a sterile, nonpyrogenic isotonic intravenous solution for injection.

After the test agent has been prepared at the clinical site, an aliquot of thawed, undiluted (if available), and diluted test agent will be titrated. Additionally, the test agent may be titrated periodically to ensure potency. The Investigational Drug Service (IDS) pharmacy will be responsible for preparing the challenge. The rDEN3Δ30 challenge will be prepared as site-of-injection formulations. Prior to inoculation, the PI/designee will supply a prescription request form to the IDS for test agent preparation that will include the protocol number, date of inoculation, dose, route of administration, test agent name, test agent lot number, test agent titer (concentration), investigational new drug (IND) number, and number of doses to be administered.

Admixture rDEN3Δ30 (3.3 $\log_{10}$ PFU/mL) will be prepared according to the site's standard operating procedures. IDS staff will prepare the correct dose of rDEN3Δ30 for each subject in a biosafety hood using aseptic technique. Test agents will be diluted with PlasmaLyte A, pH 7.4 intravenous solution, USP. The diluted challenge will be drawn up to a volume of 0.5 mL in a 1-mL syringe and labeled according to standard operating procedures. The labeled syringes will be transported at room temperature or on wet ice to the clinic for administration. Test agent must be used within 6 hours of being removed from the freezer or refrigerator.

6.3 JNJ-64281802, DENV-3 and Diluent Storage

JNJ-64281802 and placebo CCI [redacted] will be stored refrigerated in Investigational Drug Services (IDS) or at the clinic site where the agent will be administered. JNJ-64281802 and placebo CCI [redacted] will be stored ambient in Investigational Drug Services (IDS) or at the clinic site where the agent will be administered.

The rDEN3Δ30 challenge virus should remain frozen at -80°C ± 15°C until just prior to use. Test agents should never be refrozen for reuse in test article preparation. PlasmaLyte will be stored per the manufacturer's recommendation. Challenge virus and diluent components should be opened from new containers for each use. No component should be reused for future challenge preparations.

The challenge virus cannot be used until it is verified by the sponsor as acceptable for use. If the sponsor deems the challenge virus unacceptable for use, it will be quarantined until further directions from the sponsor are received. If a challenge virus is deemed unacceptable for use, it will be disposed of per the sponsor's instruction and a new shipment will be requested.

If the JNJ-64281802 test article is deemed unacceptable for use, it will be quarantined as per the pharmacy manual until further directions from the DDT are received. If the JNJ-64281802 test article is deemed unacceptable for use, it will be disposed of per the DDT's instruction and a new shipment will be requested.

6.4 JNJ-64281802, DENV-3 and Diluent Accountability

The unblinded dispenser personnel will maintain an accurate inventory and accountability record of each study agent for this study. Partially used vials of study agent or diluent components will not be refrozen or reused for future inoculations.

The investigator is responsible for ensuring that all JNJ-64281802 received at the study site is inventoried and accounted for throughout the study. The JNJ-64281802 administered to the participant must be documented on the drug accountability form.

6.5 Storage Disposition of Used/Unused Supplies

After the unblinded dispenser personnel have diluted the challenge virus and drawn up the syringes for administration, they will remove the label from the test agent vial(s) and place on the test agent preparation form. In this manner, monitoring personnel will be able to verify the accountability of all test agent vials used for the study. In addition, the number of test agent vials used will be accounted for in the study-specific drug accountability log.

An aliquot of undiluted (if available) and diluted rDEN3Δ30 will be titrated by laboratory personnel after the challenge virus has been prepared and delivered to the clinical staff. This is done to confirm the potency of the test agent administered to the subjects.

At least 1 aliquot (if available) of diluted rDEN3Δ30 will also be frozen and stored at -80°C ± 15°C at the clinical site for future re-titration if needed. After the syringes have been dispensed and aliquots removed for titration, any remaining test agent will be destroyed by the laboratory personnel per standard operating procedures. Any unused diluent from opened vials/bottles will also be destroyed.

All JNJ-64281802 will be stored and disposed of according to the pharmacy manual/study-site investigational product and procedures manual. Study-site personnel must not combine contents of the JNJ-64281802 containers.

JNJ-64281802 must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused JNJ-64281802 must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return of unused study drug will be documented on the drug return form. When the study site is authorized to destroy product and JNJ-64281802 supplies are destroyed on site, this must also be documented on the drug return form.

JNJ-64281802 should be administered under the supervision of the investigator or a qualified member of the study-site personnel. JNJ-64281802 will be administered only to participants in the study. JNJ-64281802 may not be relabeled or reassigned for use by other participants. The investigator agrees to not store JNJ-64281802 at any site other than the study site agreed upon with the DDT and to administer the study drug only at the study site. Further guidance and information for the final disposition of unused JNJ-64281802 are provided in the pharmacy manual/study site- investigational product and procedures manual.

7 Study Procedures

The following sections provide a detailed listing of the procedures and studies to be performed in this protocol at designated time points.

7.1 Recruitment and General Screening

Subjects may be recruited from a variety of sources including, but not limited to, subjects previously enrolled in trials at the clinical sites, the use of a center-wide IRB-approved screening protocol, electronic medical record recruitment messages, and/or using study-specific IRB-approved print, electronic and/or other media advertising.

After an initial phone screen (using an IRB-approved Phone Screen/Initial Contact form) by clinic staff focused on providing background information of the trial and a review of basic inclusion and exclusion criteria, a screening visit may be scheduled. Scheduling may occur manually (via phone/text with staff), or via a HIPAA-compliant electronic self-scheduling tool provided by Johns Hopkins University.

7.2 Consenting Process

During the screening process, which may require more than 1 visit, the subject will undergo a robust informed consent process. At the first screening visit, the subjects may be provided with a read-only copy of the informed consent form to take home with them. Additional materials may include a fact sheet related to dengue disease and frequently asked study questions may be provided. We encourage

our subjects to read the consent form at home prior to coming to their final screening visit. At this visit, the subject will read the consent form, be encouraged to ask questions, and then complete a comprehension assessment. The comprehension assessment is designed to test the subject's knowledge of the most pertinent and important details about the study. The subject must be able to complete the informed consent process and comprehension assessment independently and without assistance. Site specific consenting documents will be used. Study staff will review and discuss the answers from the assessment to identify those areas of the informed consent form that need further review with the subject. This robust procedure will help ensure that the subject has sufficient understanding of the study before the consent form is signed. The subject may either sign the consent form during the screening visit or return after further consideration. The subject will be encouraged to ask questions to family, friends, or anyone else at home if desired. The subject will also be provided with a signed copy of the informed consent. All study-related procedures will occur only after the informed consent is signed.

7.3 Screening Procedures

Screening for eligible participants will be performed during one or more screening visit between Day -65 and Day -6 for Cohort 1, or Day -62 and Day -3 for Cohort 2. In case the first screening visit is planned to take place within 14 days before first dose of study drug, the second screening visit may not be applicable, and all screening assessments may be performed during one single screening visit. If there are two or more screening visits some of the assessments may be repeated. A brief inclusion/exclusion criteria check is performed at screening and before the first dose of study drug on Day -5 (Cohort 1) or Day -2 (Cohort 2). An abbreviated exclusion criteria check will be performed before the challenge on Study Day 1 per section 5.3 above.

Note: The screening period between the first screening visit and the first administration of study drug may be prolonged beyond 60 days for a participant following a case-by-case evaluation and discussion with the Janssen DDT.

Subjects will undergo the following screening procedures between Study Day -65 and -6 for Cohort 1, or Study Day -62 and Day -3 for Cohort 2:

1. Explain the study and Informed Consent process to the subject.
2. Ensure that the subject has successfully completed the informed consent comprehension assessment, has signed the informed consent, and received a copy of the signed informed consent. The comprehension assessment must be completed independently and without assistance.
3. Obtain demographics.
4. COVID-19 screening questions if required per facility and/or local guidelines.
5. Nasopharyngeal (NP) or mid-turbinate swab may be collected to test for SARS-CoV 2 – the virus that causes COVID-19 will only be collected based on guidance from federal, state, local, and/or institutional health officials* or at the discretion of the clinician.

   *This guidance may be informed by the local COVID infection rate, severity of infections, vaccination rates, and other factors as the COVID-19 pandemic continues to evolve and change.

6. Ensure that HIV pre-test counseling and HIV testing have been performed and documented (within 14 days of dosing).
7. Elicit a complete medical history, including menstrual and contraceptive history, history of surgical sterilization for all subjects.
8. Review inclusion/exclusion criteria.
9. Obtain height, body weight and BMI.
10. Obtain 12 lead ECG, ideally in a supine position after greater and or equal to five minutes rest in a supine position. ECGs are recommended to be performed before vital signs and blood draw.
11. Perform a complete physical examination which includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated.
12. Obtain vital signs including (systolic and diastolic blood pressure and pulse, both obtained ideally when supine for greater than or equal to 5 minutes rest); obtain body temperature in absence of antipyretic medications.
13. Obtain approximately 15 mL of blood for the following laboratory screening tests:
    - **Cohort 1:** previous flavivirus infection of DENV or ZIKV
    - **Cohort 2:** previous flavivirus infection of DENV, ZIKV, West Nile virus, and SLEV
    - HBV
    - HCV
14. Obtain ~15.7 mL of blood for the following laboratory screening tests:
    - Complete blood count (CBC) with differential
    - Chemistry panel
        i. Sodium
        ii. Potassium
        iii. Chloride
        iv. Bicarbonate
        v. Blood urea nitrogen (BUN)
        vi. Creatinine
        vii. Glucose
        viii. Calcium
        ix. Phosphate
        x. Albumin
        xi. Total protein
        xii. Total cholesterol

xiii. Aspartate aminotransferase (AST)

xiv. Alanine aminotransferase (ALT)

xv. Gamma-glutamyltransferase (GGT)

xvi. Total bilirubin

xvii. Alkaline phosphatase

xviii. Uric acid

xix. High-density lipoprotein (HDL) cholesterol

xx. Low-density lipoprotein (LDL) cholesterol

xxi. Triglycerides

xxii. Magnesium (Cohort 1 only)

xxiii. Lipase

xxiv. Amylase

- Prothrombin time/partial thromboplastin time (PT/PTT)

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

15. Obtain urine sample for urine dipstick testing (glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrite, leukocyte esterase), if positive protein will be determined quantitively and the sediment will be examined microscopically.
16. Obtain serum for beta human chorionic gonadotropin (β-HCG) testing in persons of childbearing potential. Serum pregnancy will be performed at initial screen (Day -65 to -6 [Cohort 1] or Day -62 to -3 [Cohort 2]) and repeated at subsequent screening (if applicable).
17. Obtain 3.5 mL of blood for follicle-stimulating hormone (FSH) testing for all participants with female reproductive organs who have stopped menstruating between 12-24 months consecutively but do not have documentation, or if documentation is unobtainable, of ovarian failure by medical records.
18. May obtain medical release form to confirm method of birth control or documentation of ovarian failure (for applicable subjects).
19. Counsel persons of childbearing potential to avoid becoming pregnant during the study.
20. Assess for Concomitant Therapy.
    - In case planned first dose of study drug coincides with influenza season (typically from the beginning of October until March/April), vaccination with an influenza vaccine ≥33 days before challenge (Day -33) is strongly encouraged though not an eligibility criterion.
    - Vaccination with a COVID-19 vaccine ≥33 days before challenge (Day -33) is strongly encouraged though not an eligibility criterion.
21. May obtain alcohol breath test at the discretion of PI/provider.

22. Obtain approximately 5 mL of blood for HIV-1 and HIV-2 testing (will be performed within 14 days of initiation of JNJ-64281802). Alternatively, a rapid HIV test may be used if a Clinical Laboratory Improvement Amendments (CLIA) waiver has been granted to the site.

23. Obtain urine toxicology screening for 'drugs of abuse' including but not limited to testing for amphetamine, barbiturate, benzodiazepine, cocaine, methadone, and opiates.

7.4 Detailed Study Procedures

The study procedures to be performed at each visit are listed below. Additional tests may be done at the discretion of the PI/provider to evaluate concomitant illness or further evaluate an AE experienced by a subject.

At each visit, volunteers will be asked whether or not they have experienced any COVID-19 symptoms (per facility and/or local screening guidelines) or if they have had an exposure to someone with COVID-19 prior to coming into the clinic (per facility and/or local screening guidelines). If the volunteer reports symptoms consistent with COVID-19 and they are already enrolled in the study, an NP or mid-turbinate swab will be collected and tested for COVID-19 on site or at the respective local laboratory. If this is unavailable, the volunteer will be referred for local testing. The volunteer will not come into the clinic until the result is confirmed to be negative (~45 minutes) or per current facility guidelines for COVID-19 screening procedures. Should a volunteer test positive for SARS-CoV-2 at any point during the study, the volunteer will be asked to quarantine according to current CDC guidelines. We will review current CDC guidelines with the volunteer. We will defer all in-person visits until after the volunteer has completed their quarantine or if a COVID-19 positive research space is available they will be brought to that location.

Photographs may be taken of the injection site. In addition, photographs may be taken of other areas of the skin before and/or after inoculation to record the characteristics of any rash that may develop. To maintain participant confidentiality, possible identifiers, such as tattoos, jewelry, and clothing will not be included in the photographs whenever possible. All efforts will be taken to not identify the subject. At any point during the study participants may refuse to have their photograph taken, this will not affect their enrollment status or compensation.

The total volume of blood to be drawn over the 8-week post-inoculation period is approximately 500 mL, a little less than donating a unit of blood. This amount is within NIH guidelines (Medical Administrative Policy 95-9) for adult blood donation and should not compromise the health of study subjects. The total amount of blood drawn over the duration of the study is approximately 680 mL for Cohort 1 and 610 mL for Cohort 2. A topical anesthetic cream may be used during blood draw at the phlebotomist's discretion to ease the discomfort of the procedure.

For study visits with overlapping windows for the visit, subjects will be scheduled so that two study visits for an individual do NOT occur on the same day.

Table 3: Schedule of Procedures – Cohort 1

	Screen[5]		Dosing Study Days (Inpatient visits marked in gray)																								Follow-up Study Days							
lure	-65 to-6	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	25	29	36	43	50	57
on Visit	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
call Visit					X	X			X		X		X		X		X		X	X		X		X		X	X							

	Screen[5]		Dosing Study Days (Inpatient visits marked in gray)																								Follow-up Study Days							
dure	-65 to-6	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	23	25	29	36	43	50	57
ed Consent	X																																		
D-19 screening ns	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
review									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
mid-turbinate wab		[X][10]						[X][10]																				[X][10]							
ght Stay on Unit		X	X																																
Drug Taken			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
-3 Inoculation								X																											
al exam	X[6]		X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
igns	X	X	X	X			X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
ete Medical	X																																		
ion of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
mitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			X					X		X*		X*		X*		X*		X*			X*		X*		X*			X*							
alysis			X[3]	X				X						X		X		X					X					X[13]	X	X	X				X
tative RT-PCR							X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
tive RT-PCR																															X[3]	X	X	X	X
Assay							[X]	[X]		[X]		[X]		[X]		[X]		[X]			[X]		[X]		[X]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
LISA							X	X		X		X		X		X		X			X		X		X			X	X	X	X	X	X	X	X
IgM ELISA			X					X										X			X		X		X			X	X	X	X	X	X		X
lizing Antibody								X										X							X			X			X				
Protein Analysis			X							X						X					X				X								X		
Genome cing														[X]		[X]		[X]			[X]		[X]		[X]			[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
isolation			X													X							X								X				
NA Analysis			X							X						X					X				X								X		
Genotyping & acogenomics			X																																
																		X							X						X				X
stry Panel[9]	X		X				X					X																	X						
ith differential	X		X				X					X						X							X				X		X				X
T	X		X				X					X						X							X				X		X				X
CV, HBV	X																																		
Zikv screening	X																																		
ncy Test[1]	X		X					X																				X			X				
est[11]	X																																		
rsis & Urine ogy Screen	X																																		
l Breath Test		X[14]																																	
l ECG[8]	X		X					X																				X							

Aes = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CMP = comprehensive metabolic panel; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PT/PTT = prothrombin time/partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction

29. Serum or urine pregnancy testing only performed for persons of childbearing potential..
30. On SD -5: 7 PK samples will be collected during 16-hour window.
31. Qualitative RT-PCR will be performed on samples collected on **Days 29, 36, 43, 50, 57, 63, 70, and 85.** If the participant is DENV-3 positive detected for first time at Day ≥29, qualitative RT-PCR will be performed **twice weekly (preferably with 3 to 4 days in between samples)** until the participant results are negative and until resolution of DENV infection-associated Aes. Participants who are DENV-3 positive on Day 85 should return for additional clinical and virologic assessments until the participant results are negative and until resolution of DENV infection-associated Aes. Additional testing using different nucleic acid based methods for the detection and/or quantification of DENV-3 may be performed.
32. Phone calls to collect time of dose, time of last food, AE's, and concomitant therapy on SD -3, -2, 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, and 20.
33. Screening may occur over multiple visits. Certain procedures must be performed within different time frame relative to dosing, see Section 7.1. Screening window is Day -65 to Day -6.
34. A complete physical exam will be performed at screening and on Day 85. At all other indicated timepoints a focused physical exam will be performed.
35. [X] Sample will be collected, but test will only be performed if indicated by guidelines in the protocol.

36. **ECGs are recorded pre-dose on dosing days.**
37. Chemistry panel consists of sodium, potassium, chloride, bicarbonate, BUN, calcium, phosphate, albumin, total protein, total cholesterol, creatinine, glucose, AST, ALT, GGT, HDL cholesterol, LDL cholesterol, triglycerides, magnesium, calculated creatine clearance (by MDRD), lipase, amylase, total bilirubin, alkaline phosphatase, uric acid
38. Nasopharyngeal (NP) or mid-turbinate swab to test for SARS-CoV 2 – the virus that causes COVID-19 – will be collected from all volunteers regardless of vaccination status based on guidance from federal, state, local, and/or institutional health officials* or at the discretion of the clinician (may be collected up to 72 hours in advance of stated collection time).
    *This guidance may be informed by the local COVID infection rate, severity of infections, vaccination rates, and other factors as the COVID-19 pandemic continues to evolve and change. NP or mid-turbinate swabs may be collected at other time-points if volunteer has COVID-like symptoms.
39. FSH performed only in females who have stopped menstruating for > 12 consecutive months but < 24 months. (Anyone who has had amenorrhea > 24 consecutive months is considered postmenopausal and does not require FSH).
40. In participants who develop a rash, an additional sample will be collected at onset of rash and tested. Noted on this chart with an asterisk {X*}
41. On Study Day 21: 6 PK samples will be collected during a 12-hour window
42. Alcohol breath test may be performed at the discretion of PI/provider upon admission to inpatient unit

Table 3 summarizes the frequency and timing of antiviral activity, PK, biomarker, pharmacogenomic, and safety measurements applicable to this study. Table 4 provides this information for Cohort 2.

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

Additional NP or mid-turbinate swabs may be collected, as determined necessary by the COVID-19 screening questionnaire throughout the course of the study and local/facility screening guidelines, to establish the absence of infection with SARS-CoV 2.

7.5 Safety Assessments

Safety and tolerability will be evaluated throughout the study from signing of the ICF 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.

DENV infection-associated AEs will be measured using the following parameters: time to resolution and severity of the DENV infection-associated AEs. These are defined as systemic reactions and will be recorded as solicited AEs by the investigator in the electronic case report forms (eCRFs) (see Table 13 for complete list). DENV infection-associated AEs will be monitored at each visit by the investigator or designee as solicited AEs to assess whether inpatient admission criteria are met (section 7.18). Body temperature will be recorded twice daily by study staff and/or by the participants from Day 1 up to and including Day 29 using the provided thermometer and dengue memory enhancement card. In case of fever on Day 29, participants will be instructed to record their body temperature daily until resolution. Participants who report DENV infection-associated AEs on or after Day 29, will be instructed to return to the study site for a clinical evaluation, safety laboratory assessments, and qualitative RT-PCR testing. In case the observed DENV infection-associated AEs, clinical assessments, or dengue-specific laboratory parameters (ie, platelet count, white blood cell count, prothrombin time, and hematocrit) are > Grade 2 in severity, with or without detectable DENV-3 RNA, the participant will be followed-up on an outpatient basis by daily telephone calls conducted by the study-site personnel until resolution of the DENV infection associated- AEs. Dengue-specific laboratory parameters will be evaluated until documented resolution.

The study will include the following evaluations of safety and tolerability according to the time points provided in section 7.4:

- AEs
- Clinical laboratory tests
- Vital signs
- Physical examination

Any clinically relevant changes occurring during the study must be recorded in the Adverse Event section of the case report forms (CRF).

7.6 Antiviral Activity Assessments

At time points specified in Table 3 (Cohort 1) and Table 4 (Cohort 2), blood samples will be obtained for measurement of levels of:

- DENV-3 RNA
- Viremia (ie, infectious DENV-3)
- DENV-3 NS1 protein (required for Cohort 1; analysis optional for Cohort 2)

DENV-3 RNA serum levels will be assessed using a validated quantitative DENV-3 RT-PCR assay. Qualitative RT-PCR will also be performed. If the participant is DENV-3 positive *detected at Day ≥29 in Cohort 1, qualitative RT-PCR will be performed* ***twice weekly*** *until the participant results are negative and until resolution of DENV infection-associated AEs.*

For Cohort 2, if a participant is positive for the on Day ≥25 (or day 23 if day 25 not available), additional visits on Day 27 and Day 34 should occur, ***meaning 2-3 days sampling*** *is required.* Participants who are DENV-3 positive by qualitative RT-PCR on Day 85 should return for additional clinical and virologic assessments until the participant results are negative and until resolution of DENV infection associated AEs. Additional testing using different nucleic acid-based methods for the detection and/or quantification of DENV-3 may be performed. DENV-3 viremia will be determined using an assay for infectious virus quantification *such as a plaque assay*. In addition, antiviral activity may be explored by assessing NS1 protein using an enzyme-linked immunosorbent assay (ELISA)-based assay and/or an NS1 test, which are designed for point-of-care use (eg, immunochromatography-based methods). *Details of the assays used will be provided in the laboratory manual*.

The changes in DENV-3 VL will not be reported as AEs or SAEs.

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of the DENV-3 infection and the antiviral activity of the study drug, including viral genotypic and phenotypic assessments.

7.7 Pharmacokinetic Assessments

7.7.1 Sample Collection and Handling

Venous blood samples will be taken for measurement of plasma concentrations of JNJ-64281802 at the time points indicated in Table 3 (Cohort 1) and Table 4 (Cohort 2). Additional PK sampling may be performed on the non-intensive PK days (eg, in the event of an overdose) on other time points, in consultation with the Janssen drug development team. The exact dates and times of blood sampling must be recorded in the CRF or laboratory requisition form.

Cohort 1: On Study Day -5 and Day 21, PK samples will be collected within the 2 hours prior to dosing with JNJ-64281802 as well as 1, 2, 4, 8, 12, 16 (at study day -5 only) and 24 hours (at study day -5 only) after dosing. On all other study days where PK samples are collected, a single blood collection will occur prior to dosing with JNJ-64281802.

Cohort 2 Daily Dosing: On Study Day -2 and Day 21, PK samples will be collected within the 2 hours prior to dosing with JNJ-64281802 as well as 1, 2, 4, 8, and 12 hours after dosing. On Study Day -2, PK samples will also be collected 16 and 24 hours after dosing. On all other study days where PK samples are collected, a single blood collection will occur prior to dosing with JNJ-64281802 (if applicable).

Cohort 2 Weekly Dosing: On Study Day -2 and Day 15, PK samples will be collected within the 2 hours prior to dosing with JNJ-64281802 as well as 1, 2, 4, 8, and 12 hours after dosing. On Study Day -2, PK samples will also be collected 16 and 24 hours after dosing. On all other study days where PK samples are collected, a single blood collection will occur prior to dosing with JNJ-64281802 (if applicable).

The following need to be recorded in the CRF:

Cohort 1:

- Date and time of dosing with study drug on the day of the PK blood sampling.
- Whether study drug was taken with food on the day of PK blood sampling.
- Date and time of last meal before dosing with study drug on the day of PK blood sampling.
- Date and time of the first meal after dosing with study drug on Day -5 and 21.
- Date and time of last water intake before dosing with study drug on Day -5 and Day 21.

Cohort 2:

- Date and time of PK blood sampling
- Date and time of dosing with study drug
- Whether study drug was taken with food
- Date and time of last meal before dosing with study drug

7.7.2 Pharmacokinetic Analysis

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

Pharmacokinetic samples from participants assigned to placebo (except for samples taken pre-dose on Day -5 [Cohort 1] or Day -2 [Cohort 2]) will not be analyzed unless unexpected results should occur. All plasma PK samples from participants receiving JNJ-64281802 will be analyzed for JNJ-64281802 concentrations.

To allow selection of samples, the bioanalytical laboratory will receive randomization lists per treatment. Unblinding of the randomization code will be performed at the bioanalytical laboratory only and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the conduct of the study. No one outside of the lab will have access to this information until the study is fully unblinded.

At the DDT's discretion, plasma samples may be analyzed for circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future exploratory analysis of protein binding, biomarkers, and the metabolite profile.

7.7.3 Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual sampling times (section 9.5), at least the following PK parameters will be derived for JNJ-64281802:

Cohort 1:

- On Day -5: C_{max}, t_{max}, AUCτ and C_{avg}.
- On Days -4 to Day 20: C_{trough} (on days when blood sampling for PK is conducted).
- On Day 21: C_{trough}, C_{min}, C_{max}, t_{max}, AUCτ, C_{avg}, and FI.

Cohort 2 Daily Regimen:

- On Day -2: C_{max}, t_{max}, AUCτ and C_{avg}.
- On Days -1 to Day 20: C_{trough} (on days when blood sampling for PK is conducted: -1, 1, 4, 8, 11, 15, 18).
- On Day 21: C_{trough}, C_{min}, C_{max}, t_{max}, AUCτ, C_{avg}, and FI.

Cohort 2 Weekly Regimen:

- On Day -2: C_{max}, t_{max}, AUCτ and C_{avg}.
- On Days -1 to Day 11: C_{trough} (on days when blood sampling for PK is conducted: -1, 1, 4, 8, 11).
- On Day 15: C_{trough}, C_{min}, C_{max}, t_{max}, AUCτ, C_{avg}, and FI.

For the PK parameters, definitions and methods of calculation are:

- C_{max}: maximum observed analyte concentration;
- C_{min}: minimum observed analyte concentration;
- C_{trough}: observed analyte concentration just before the beginning or at the end of a dosing interval;
- C_{avg}: average analyte concentration over the dosing interval (τ) calculated as $AUC_{\tau/\tau}$;
- t_{max}: the actual sampling time to reach the maximum observed analyte concentration;
- FI: percentage fluctuation (variation) between maximum and minimum analyte concentration at steady-state, calculated as 100 x ([C_{max} - C_{min}] / C_{avg});
- AUC_{τ}: area under the plasma concentration-time curve during the dosing interval (t hours); calculated by linear-linear trapezoidal summation.

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

7.8 Immune Assessments

Blood samples for the assessment of humoral and cellular immune responses will be collected from all participants according to the time points indicated in Table 3 (Cohort 1) and Table 4 (Cohort 2).

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

7.8.1 Humoral Immune Response

Blood samples will be obtained for the assessment of serum antibody responses. Anti-DENV-3 IgG and IgM antibodies will be measured using ELISA. The presence of neutralizing antibodies against DENV may be determined using a plaque reduction neutralization assay or flow cytometry-based assay using standard laboratory protocols. The $PRNT_{50}$ is defined as the highest dilution of antibody that reduces the number of foci or plaques by 50%, compared to the plaque titer of the virus alone. Analysis will be optional for Cohort 2.

Serum samples for in vivo research (to investigate potential JNJ-64281802-specific IgE induced myeloid cell degranulation) will be analyzed in participants who develop rash during the study. Samples will be collected from all participants predose at Day -5 for Cohort 1, Day -2 for Cohort 2, and prechallenge at Day 1 for both cohorts. In participants who develop rash, the sample will be repeated when the rash is observed.

7.8.2 Cellular Immune Response

Peripheral blood mononuclear cell (PBMC) samples may be analyzed to assess DENV-3-specific T and B cell immune responses using assays such as enzyme-linked immunospot assay (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with DENV-3-specific antigens. ELISpot detects T cells that secrete interferon gamma (IFN-γ) or B cells that secrete IgG and/or IgM, whereas ICS determines the frequency of CD4+ and CD8+ T cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs by methods such as flow cytometry, mass cytometry (CyTOF), or single cell transcriptomics to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research related to DENV infection or JNJ-64281802 (safety/antiviral activity).

7.9 Biomarker Assessments

Blood sampling for biomarker analyses will be performed at the time points indicated in Table 3 for Cohort 1 and Table 4 for Cohort 2.

Samples for host RNA might be used for transcriptional profiling (eg, using microarray technology). Serum samples for protein analyses might be analyzed using assays such as ELISA or Luminex. Prostaglandins and leukotrienes may be measured using an ELISA.

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

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

7.10 Viral Genome Sequencing

Blood sampling for viral genome sequencing analysis will be performed at the time points indicated in Table 3 for Cohort 1 and Table 4 for Cohort 2. Viral genome sequencing may be performed if DENV RNA-3 is positive considering the limits of the sequencing assay.

Sequencing of the DENV-3 genome will be performed to monitor DENV-3 variants. Viral genome sequencing analysis will be performed by sequencing the NS3 and NS4B genes and other regions of the DENV-3 genome (if warranted) to characterize emerging DENV-3 variants associated with resistance to JNJ-64281802 compared with the sequence of the rDEN3Δ30 strain used for inoculation. Participants who received JNJ-64281802 or placebo will be analyzed.

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of DENV-3 infection and antiviral activity and safety of JNJ-64281802, including viral genotypic and phenotypic assessments.

7.11 Human Leukocyte Antigen Typing and Pharmacogenomic Evaluations

A blood sample for HLA genotyping and for pharmacogenomic research will be collected at baseline (ie, before first dose of study drug), to determine the HLA type of each participant and to allow the identification of genetic factors that may influence the PK, antiviral activity, or safety/tolerability of JNJ-64281802. HLA genotyping and pharmacogenomic (DNA) research may help to explain interindividual variability in clinical outcomes and identify population subgroups that respond differently to a drug. Participation in the HLA typing and the pharmacogenomic research is mandatory.

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

7.12 Inoculation with rDEN3Δ30

The DENV-3 investigational challenge material is rDEN3Δ30 (Lot DEN3#114A) composed of a concentration of live, recombinant rDEN3Δ30 Vero Grown Virus Vaccine, in L-15 medium containing 1X SPG. The potency of rDEN3Δ30 (Lot DEN3 #114A) is 6.1 $\log_{10}$ PFU/mL. Subjects will receive rDEN3Δ30 on Study Day 1. The live rDEN3Δ30 viruses will be kept frozen at -80°C ± 15°C until just before use, at which time they will be thawed, diluted, and drawn up for administration. rDEN3Δ30 is diluted with Plasma-lyte A, pH 7.4 intravenous solution, USP to the final concentration of 3 $\log_{10}$ PFU/0.5 mL in a 1-mL syringe for SC injection. rDEN3Δ30 will be kept on wet ice from the time it is thawed or removed from the refrigerator until diluted with Plasma-lyte into its final formulation. It will then be delivered at room temperature or on wet ice to clinical staff for administration. A volume of 0.5 mL of rDEN3Δ30 will be delivered by SC injection in the deltoid region of the upper arm with a needle of appropriate gauge and length after wiping the injection site with alcohol. On Day 1, participants will be inoculated with rDEN3Δ30 30 to 60 minutes after administration of study drug.

7.13 Scheduled Admission to the Inpatient Unit

Cohort 1: Subjects will be admitted to the inpatient unit on Study Day -6 through the study visit on Study Day -4 due to the intensive PK sampling during these time points. On the day of admission to the inpatient unit on Study Day -6, more subjects may be invited to the clinic than will be enrolled. These subjects will be alternates and will be randomized and receive JNJ-64281802 or placebo only if other subjects are not available to receive study product or are found to be ineligible on the day of test article administration (Study Day -5). Those subjects who are alternates will be informed that they are alternates when they are invited to the clinic.

Cohort 2: Subjects will be admitted to the inpatient unit on Study Day -3 through the study visit on Study Day 1 due to the intensive PK sampling during these time points. On the day of admission to the inpatient unit on Study Day -3, more subjects may be invited to the clinic than will be enrolled. These

subjects will be alternates and will be randomized and receive JNJ-64281802 or placebo only if other subjects are not available to receive study product or are found to be ineligible on the day of test article administration (Study Day -2). Those subjects who are alternates will be informed that they are alternates when they are invited to the clinic.

7.14 Medication Administration of JNJ-64281802

Participants will receive study drug (ie, JNJ-64281802 or placebo) as described in Table 12. CCI [redacted]. Dosing regimens for Cohort 2 were selected based on the safety, efficacy, and PK findings of Cohort 1 and on the relationship between the PK and the antiviral activity obtained from the Cohort 1 interim results analysis.

Table 12: Description of Study Drug

Study Drug	JNJ-64281802	Placebo
CCI [redacted]	CCI [redacted]	CCI [redacted]
CCI [redacted]	C [redacted]	Matching placebo for each dose level
Dosage level(s)	**Cohort 1:** • Group 1: 600 mg (LD)/200 mg (MD) once daily • Group 2: 40 mg (LD)/10 mg (MD) once daily or 200 mg (LD)/50 mg (MD) once daily **Cohort 2:** • Group 3 : 800 mg (LD) twice daily / 250 mg (MD) once daily • Group 4 : 450 mg (LD) twice daily / 1200 mg (MD) weekly • Group 5 : 250 mg (LD) twice daily / 500 mg (MD) weekly	**Cohort 1:** matching placebo once daily. **Cohort 2:** • Matching placebo twice daily (loading dose period) for all regimens. • Matching placebo once daily (maintenance dose period Group 3) or weekly (maintenance dose period Groups 4, 5)

Study Drug	JNJ-64281802	Placebo
CCI [redacted]	CCI [redacted]	CCI [redacted]
Route of administration	Oral	Oral
Dosing duration	**Cohort 1:** 26 days (from Day -5 to Day 21); LD period of 5 days (Days -5 to -1) followed by a MD period of 21 days (Days 1 to 21). **Cohort 2**: • Daily dosing: 23 days (from Day -2 to Day 21); LD period of 2 days (Days -2 to -1) followed by a MD period of 21 days (Days 1 to 21). • Weekly dosing: LD period of 2 days (Days -2 to -1) followed by a MD on Day 1, Day 8, and Day 15 (period of 3 weeks)	
Location	All study drug intake will take place at the study site, at the inpatient unit in case of inpatient admission, or self administration at home	
Time of Dosing	In the morning (6 AM to 12 PM), each day. Cohort 2: Loading doses will be given twice daily (approximately 12 hours apart).	
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the DDT.	Provided centrally by the DDT.

Study Drug	JNJ-64281802	Placebo
Food/fasting requirement	**Cohort 1:** On Days -5 and 21, participants should have fasted for at least 10 hours before study drug intake and have lunch approximately 4 hours after study drug intake. Thus, breakfast is not allowed on these days. On the other dosing days, participants should have fasted for at least 8 hours before study drug intake and have breakfast at least 1 hour after study drug intake. On Day -5 and Day 21, intake of water is not allowed from 2 hours before until 2 hours after study drug intake, except for the water used for study drug intake. **Cohort 2:** The study intervention is to be taken in fed conditions, ie, within 30 minutes after the start of the participant's regular meal, as applicable. Study drug intake can be followed by the intake of approximately 240 mL (8 ounces) of noncarbonated water. The tablets should be swallowed intact.	
Packaging and labeling	Study drug will be provided in child-resistant HDPE bottles (ie, not packaged for individual participant numbers). Each container will contain information and be labeled as required per country regulatory requirements. Labels must remain affixed to the container.	

A = active; HDPE = high-density polyethylene; CCI ; IMP = investigational medicinal product; LD = loading dose; MD = maintenance dose; NIMP = noninvestigational medicinal product; P = placebo.

7.15 Anticipated Inpatient Stay and Follow Up Procedures

During the anticipated inpatient stay, the subject will have vital signs (blood pressure, heart rate, and oral temperature) taken twice a day. A focused physical examination will be performed each day while inpatient (excluding Cohort 1 Day -6 and Cohort 2 Day -3) and at designated outpatient visits. A focused physical exam may include, but is not limited to, blood pressure, heart rate, temperature, skin examination and oropharynx examination. Additional physical exam components or physical examinations on additional study days may be done if clinically indicated at the provider's discretion.

Table 3 summarizes the frequency and timing of antiviral activity, PK, immune, biomarker, HLA genotyping and pharmacogenomic, and safety measurements applicable to this study for Cohort 1. Table 4 provides this information for Cohort 2. Additionally, detailed information for study visits is provided in section 7.16 for Cohort 1 and section 7.17 for Cohort 2.

If multiple assessments are scheduled at the same time point, it is recommended to adhere to following order of assessments: 12-lead ECG(s), vital signs, blood draw. Blood collections for PK and antiviral activity assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than the specified time points if needed. Actual dates and times of assessments must be recorded in the source documentation and CRF.

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

7.16 Cohort 1 Schedule of Procedures

The study schedule is also outlined in Table 3.

Cohort 1 Study Day -6 *(Admission to Inpatient Unit)*

Participants will stay in-house during the intensive PK sampling period from Day -6 until at least 24 hours post first dose (ie, the morning of Day -4).

1. Screening questions for COVID-19 (per facility screening guidelines).

2. A NP or mid-turbinate swab to test for COVID-19 may be collected if determined necessary by the clinician or per guidelines, (the swab may be obtained up to 72 hours in advance of study visit).
3. Admit to inpatient unit.
4. Verify that informed consent was obtained and that the consent form was signed by both the subject and study staff.
5. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
6. Review pregnancy prevention with the subject.
7. Review and document concomitant therapy.
8. Review and document AEs.
9. Review inclusion and exclusion criteria.

Cohort 1 Study Day -5 *(Begin JNJ-64281802 Test Article Administration)*

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Verify that all applicable eligibility criteria have been met.
3. Stop water intake two hours prior to administration of study drug. *Intake of water is not allowed from 2 hours before until 2 hours after study drug intake, except for the water used for study drug intake.* Record last water intake, and when water intake is restarted following study drug administration.
4. Record last food intake. *Last food intake should be 10 hours prior to study drug administration, and first food intake should be at least 4 hours after study drug administration.*
5. Perform 12-Lead ECG prior to dosing, *should be performed in supine position, after ≥5 minutes rest in supine position.*
6. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication). Vital signs will be assessed pre-dose and 8 hours post-dose.
7. Perform interim history and focused physical exam, concentrating on any acute complaints.
8. Review and document concomitant therapy.
9. Review and document AEs.
10. For applicable persons of childbearing potential, perform β-HCG testing. Ensure the test is negative before proceeding with study drug administration. A positive test will exclude the subject from the study see section 5.2.
11. Prior to study drug administration, obtain approximately ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel. *These laboratory studies are drawn as baseline values and will not determine eligibility.*
12. Blood sample collection for PK analysis. Obtain ~3 mL of blood for pre-dose PK analysis within the 2 hours prior to dosing with study drug. An additional ~3 mL of blood will be collected for PK analysis at the following timepoints post administration with study drug: +1 hour, +2 hours, +4 hours, +8 hours, +12 hours, and +16 hours.
13. Prior to study drug administration, collect ~15 mL of blood for IgG & IgM ELISA, IgE analysis, and serum protein analysis.
14. Prior to study drug administration, collect ~30 mL of blood for cellular immunity (PBMC) analysis and HLA genotyping and pharmacogenomics.
15. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
16. Administer loading dose of the study drug, JNJ-64281802/placebo.

17. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.
18. Resume water intake approximately 2 hours after study drug intake.
19. Adhere to standard lunch, afternoon snack and dinner dietary restrictions. Record start and stop times of all food intake. *Standard lunch will start approximately 4 hours post dose (right after PK sampling at +4h post dose has been performed). Standard afternoon snack will start approximately7 hours post dose. Standard dinner will start approximately 10 hours post dose.* All start and stop times of intake of food should be recorded on Study Day -5.
20. Provide education by study staff on the signs and symptoms of potential AEs, and how and when to contact study staff.
21. Distribute wallet card with investigator contact information and post-study DHCM medical statement.

Cohort 1 Study Day -4 (*Discharge from Inpatient Unit*)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake. *Last food intake should be standard dinner on Study Day -5, participant should have fasted for at least 8 hours prior to study drug administration.*
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document concomitant therapy.
6. Review and document AEs.
7. Collect ~3mL of blood for PK analysis. This blood collection should occur prior to administration of study drug on Study Day -4, and approximately 24 hours following administration of study administration on Study Day -5.
8. Administer loading dose of the study drug, JNJ-64281802/placebo.
9. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.
10. Resume normal food intake at least 1 hour following study drug intake on Study Day -4 and approximately 24 hours after study drug intake on Day -5.

Cohort 1 Study Day -3 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record time subject self-administered loading dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day -2 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record time subject self-administered loading dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day -1 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document concomitant therapy.
6. Review and document AEs.
7. Prior to study drug administration, collect ~10.0 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1).
8. Prior to study drug administration, collect ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel.
9. Administer loading dose of the study drug, JNJ-64281802/placebo.
10. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.
11. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 1 (Outpatient challenge with DENV-3)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. A NP or mid-turbinate swab to test for COVID-19 may be collected if determined necessary by the clinician or per guidelines, (the swab may be obtained up to 72 hours in advance of study visit).
3. For applicable persons of childbearing potential, perform β-HCG testing. Ensure the test is negative before proceeding; a positive test will exclude the subject from the study as per protocol, section 5.3.
4. Review pregnancy prevention with the subject.
5. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
6. Verify that all applicable eligibility criteria for challenge with DENV-3 have been met, see section 5.
7. Perform 12-Lead ECG, *should be performed in supine position, after ≥5 minutes rest in supine position.*
8. Record predose vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
9. Perform interim history and focused physical exam, concentrating on any acute complaints.
10. Review and document concomitant therapy.
11. Review and document AEs.
12. Prior to study drug administration, collect ~3 mL of blood for PK analysis.
13. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1) and humoral immunity (IgG, IgM, neutralizing antibody), and IgE testing.
14. Administer maintenance dose of the study drug, JNJ-64281802/placebo. *Study drug intake should take place 30 to 60 minutes before DENV-3 inoculation.*

15. Administer a single SC injection with a recombinant DENV-3 strain.
16. Evaluation of the injection site.
17. Observe for at least 30-minutes after dosing/challenge and evaluate for immediate hypersensitivity.
18. Record temperature and any local reactogenicity at least 30 minutes post challenge.
19. Distribute Dengue Memory Enhancement Card (DMEC) to subjects
20. Provide education by study staff describing the proper use of the thermometer, the signs and symptoms of potential AEs, and how and when to contact study staff.
21. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 2 (phone visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 3 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Prior to study drug administration, collect ~10.0 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1) and serum protein analysis.
9. Prior to study drug administration, collect ~2.5 mL for host RNA assessments.
10. Perform evaluation of the injection site.
11. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
12. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 4 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 5 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
3. Record vital signs (Systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Perform evaluation of the injection site.
9. Prior to study drug administration, collect ~15.0 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1).
10. Prior to study drug administration, collect ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel.
11. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
12. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 6 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 7 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
3. Record vital signs (Systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Perform evaluation of the injection site.
9. Prior to study drug administration, collect ~3 mL of blood for PK analysis
10. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1), and viral genome sequencing.
11. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
12. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 8 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 9 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Prior to study drug administration, collect ~ 3 mL of blood for PK analysis
9. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1), serum proteins and viral genome sequencing.
10. Prior to study drug administration, collect ~30mL of blood for cellular immunity (PBMC) analysis.
11. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
12. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
13. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 10 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 11 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute

complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Prior to study drug administration, collect ~ 3 mL of blood for PK analysis.
9. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG, IgM, & neutralizing antibody), and viral genome sequencing.
10. Prior to study drug administration, collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.
11. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
12. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 12 (phone contact visit)
1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 13 (phone contact visit)
1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration.*
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 14 (on site visit)
1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), serum proteins and viral genome sequencing.
9. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
10. Administer maintenance dose of the study drug, JNJ-64281802/placebo.

11. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 15 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 16 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitanttherapy.
8. Prior to study drug administration, collect ~3 mL of blood for PK analysis.
9. Prior to study drug administration, collect ~30 mL of blood for cellular immunity (PBMC)
10. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), and viral genome sequencing.
11. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
12. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 17 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 18 (on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.

5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG, IgM, & neutralizing antibody), serum protein analysis and viral genome sequencing.
9. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
10. Prior to study drug administration, collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.
11. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
12. Subject should wait to resume normal food intake for at least 1 hour following study drug administration.

Cohort 1 Study Day 19 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 20 (phone contact visit)

1. Record last food intake, *subject should have fasted for at least 8 hours prior to study drug administration*.
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record time subject self-administered maintenance dose of the study drug, JNJ-64281802/placebo.

Cohort 1 Study Day 21 (entire day clinic visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. A NP or mid-turbinate swab to test for COVID-19 may be collected if determined necessary by the clinician or per guidelines, (the swab may be obtained up to 72 hours in advance of study visit).
3. Stop water intake two hours prior to administration of study drug. *Intake of water is not allowed from 2 hours before until 2 hours after study drug intake, except for the water used for study drug intake.* Records last water intake, and when water intake is restarted following study drug administration.
4. Record last food intake. *Last food intake should be 10 hours prior to study drug administration, and first food intake should be at least 4 hours after study drug administration.*
5. Review DMEC.
6. Perform 12 Lead ECG, *should be performed in supine position, after ≥5 minutes rest in supine position.*

7. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication). On Day 21, vital signs will be assessed pre-dose and 8 hours post-dose. *When scheduled for the same timepoint, vital signs should be assess*sed before blood draw.
8. Perform interim history and focused physical exam, concentrating on any acute complaints.
9. Review and document AEs.
10. Review and document concomitant therapy.
11. Blood sample collection for PK analysis. Obtain ~3 mL of blood for pre-dose PK analysis within the 2 hours prior to dosing with study drug. An additional ~3 mL of blood will be collected for PK analysis at the following timepoints post administration with study drug: +1 hour, +2 hours, +4 hours, +8 hours, and +12 hours.
12. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG, IgM, & neutralizing antibody) and viral genome sequencing.
13. For applicable persons of childbearing potential, perform β–HCG testing
14. Administer maintenance dose of the study drug, JNJ-64281802/placebo.
15. Resume water intake approximately 2 hours after study drug intake.
16. Adhere to standard lunch, afternoon snack and dinner dietary restrictions. Record start and stop times of all food intake. *Standard lunch will start approximately 4 hours post dose (right after PK sampling at +4h post dose has been performed). Standard afternoon snack will start approximately 7 hours post dose. Standard dinner will start approximately 10 hours post dose.* All start and stop times of intake of food should be recorded on Study Day 21.

Cohort 1 Study Day 23 (+1/-1 days, on site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record vital signs (Systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
6. Perform interim history and focused physical exam, concentrating on any acute complaints.
7. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), and viral genome sequencing.
8. Collect ~3 mL blood for PK analysis
9. Collect ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel.

Cohort 1 Study Day 25 (+1/-1 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
6. Perform interim history and focused physical exam, concentrating on any acute complaints.

7. Collect ~3 mL of blood for PK analysis.
8. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay NS1), humoral immunity (IgG & IgM), and viral genome sequencing.

Cohort 1 Study Day 29 (+1/-1 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review DMEC.
3. Review and document AEs.
4. Review and document concomitant therapy.
5. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
6. Perform interim history and focused physical exam, concentrating on any acute complaints.
7. For applicable persons of childbearing potential, perform β-HCG testing.
8. Review pregnancy prevention with the subject.
9. Collect ~30 mL of blood for PBMCs
10. Collect ~15 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG, IgM, & neutralizing antibody), and viral genome sequencing.
11. Collect ~3 mL of blood for PK analysis.
12. Collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.

Cohort 1 Study Day 36 (+2/-2 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG & IgM), and viral genome sequencing.

Cohort 1 Study Day 43 (+2/-2 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review and document AEs
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect 10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG & IgM), serum proteins and viral genome sequencing.

Cohort 1 Study Day 50 (+2/-2 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).

2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect ~10.0 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1), qualitative PCR, and viral genome sequencing.
7. Collect ~2.5 mL of blood for host RNA assessments.

Cohort 1 Study Day 57 (+2/-2 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Review pregnancy prevention with the subject.
5. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
6. Perform interim history and focused physical exam, concentrating on any acute complaints.
7. Collect ~3 mL of blood for PK analysis.
8. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG & IgM), and viral genome sequencing.
9. Collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.

Cohort 1 Study Day 63 (+2/-2 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, & NS1), qualitative PCR and viral genome sequencing.

Cohort 1 Study Day 70 (+2/-2 days, on-site visit)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect ~3 mL of blood for PK analysis.
7. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG, IgM, & neutralizing antibody), serum proteins and viral genome sequencing.

Cohort 1 Study Day 85 (+3/-3 days, End of Study)

1. Screening questions for COVID-19 (per facility screening guidelines).
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform 12-Lead ECG, *should be performed in supine position, after ≥5 minutes rest in supine position.*
6. Perform interim history, concentrating on any acute complaints, and complete physical exam.
7. Obtain weight.
8. Perform complete physical examination.
9. For applicable persons of childbearing potential, perform β-HCG testing.
10. Review pregnancy prevention with the subject.
11. Collect ~3 mL of blood for PK analysis.
12. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG, IgM, & neutralizing antibody), serum proteins and viral genome sequencing.
13. Collect ~30 mL of blood for cellular immunity (PBMC).
14. Collect ~2.5 mL of blood for host RNA assessments.

7.17 Cohort 2 Schedule of Procedures

The study schedule for Cohort 2 is also outlined in Table 4. Participants in the weekly dosing group have the same number of visits after discharge from the inpatient unit, however, they only receive study drug on Days 8 and 15. Visit activities that occur "prior to study drug administration" for the daily dose groups also apply to the weekly dose group, even when no dose is given.

Cohort 2 Study Day -3 (*Admission to Inpatient Unit*)

Participants will stay in-house during the intensive PK sampling period from Day -3 until at least 24 hours post first dose (ie, the morning of Day 1).

1. Screening questions for COVID-19 (per facility screening guidelines).
2. A NP or mid-turbinate swab to test for COVID-19 may be collected if determined necessary by the clinician or per guidelines, (the swab may be obtained up to 72 hours in advance of study visit).
3. Alcohol breath test (PI discretion).
4. Admit to inpatient unit.
5. Verify that informed consent was obtained and that the consent form was signed by both the subject and study staff.
6. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
7. Review pregnancy prevention with the subject.
8. Review and document concomitant therapy.
9. Review and document AEs.
10. Review inclusion and exclusion criteria.

Cohort 2 Study Day -2 (*Begin JNJ-64281802 Test Article Administration*)

1. Verify that all applicable eligibility criteria have been met.

2. Record last food intake.
   Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake.
3. Perform 12-Lead ECG prior to dosing, *should be performed in supine position, after ≥5 minutes rest in supine position.*
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication). Vital signs will be assessed pre-dose and 8 hours post-dose.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document concomitant therapy.
7. Review and document AEs.
8. For applicable persons of childbearing potential, perform β-HCG testing. Ensure the test is negative before proceeding with study drug administration. A positive test will exclude the subject from the study, see section 5.2.
9. Prior to study drug administration, obtain approximately ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel. *These laboratory studies are drawn as baseline values and will not determine eligibility.*
10. Blood sample collection for PK analysis. Obtain ~3 mL of blood for pre-dose PK analysis within the 2 hours prior to dosing with study drug. An additional ~3 mL of blood will be collected for PK analysis at the following timepoints post administration of the study drug: +1 hour, +2 hours, +4 hours, +8 hours, +12 hours, and +16 hours. Record time of blood samples. Note the second dose of study drug should be administered after the 12 hour PK draw per Table 4 footnote.
11. Prior to study drug administration, collect ~15 mL of blood for DENV IgG & IgM ELISA, IgE analysis, neutralizing antibodies, and serum protein analysis.
12. Prior to study drug administration, collect ~30 mL of blood for cellular immunity (PBMC) analysis and HLA genotyping and pharmacogenomics.
13. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
14. Prior to study drug administration, collect ~3 mL for A1AG assessment.
15. Administer loading dose of the study drug, JNJ-64281802/placebo. Record time of administration.
16. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.
17. Administer second loading dose of study drug, JNJ-64281802/placebo approximately 12 hours after initial dose. Second dose should be given AFTER the 12 hour PK draw per Table 4 footnote. Standard meal within 30 minutes prior to drug intake. Record time of meal and time of study drug administration. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.
18. Adhere to standard lunch, afternoon snack, and dinner dietary restrictions.
    Standard meal is taken within 30 min prior to drug intake.

Cohort 2 Study Day -1 (*Inpatient*)

1. Record last food intake.
   Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).

3. Perform interim history and focused physical exam, concentrating on any acute complaints.
4. Review and document concomitant therapy.
5. Review and document AEs.
6. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, and NS1).
7. Collect ~3 mL of blood for PK analysis. This blood collection should occur prior to administration of study drug on Study Day -1, and approximately 24 hours following administration of study administration on Study Day -2. Record time of blood sample.
8. Prior to study drug administration, collect ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel.
9. Prior to study drug administration, collect ~3 mL for A1AG assessment
10. Administer loading dose of the study drug, JNJ-64281802/placebo. Record time of administration.
11. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.
12. Administer second loading dose of study drug, JNJ-64281802/placebo approximately 12 hours after initial dose. Standard meal within 30 minutes prior to drug intake. Record time of meal and time of study drug administration. Observe for at least 30 minutes after study drug administration and evaluate for immediate hypersensitivity.

Cohort 2 Study Day 1 (*Challenge with DENV-3, Discharge from Inpatient Unit*)

1. For applicable persons of childbearing potential, perform β-HCG testing. Ensure the test is negative before proceeding; a positive test will exclude the subject from the study as per protocol, section 5.3.
2. Review pregnancy prevention with the subject.
3. Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake.
4. Verify that all applicable eligibility criteria for challenge with DENV-3 have been met, see section 5.
5. Perform 12-Lead ECG prior to dosing, *should be performed in supine position, after ≥5 minutes rest in supine position.*
6. Record predose vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
7. Perform interim history and focused physical exam, concentrating on any acute complaints.
8. Review and document concomitant therapy.
9. Review and document AEs.
10. Prior to study drug administration, collect ~3 mL of blood for PK analysis. Record time of blood sample.
11. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, and NS1) and humoral immunity (IgG and IgM; neutralizing antibody), and IgE testing.
12. Prior to study drug administration, collect ~3 mL for A1AG assessment
13. Administer maintenance dose of the study drug, JNJ-64281802/placebo. *Study drug intake should take place 30 to 60 minutes before DENV-3 inoculation.* Record time of administration.
14. Administer a single SC injection with a recombinant DENV-3 strain.

15. Evaluation of the injection site.
16. Observe for at least 30 minutes after dosing/challenge and evaluate for immediate hypersensitivity.
17. Record temperature and any local reactogenicity at least 30 minutes post challenge.
18. Provide education by study staff describing the proper use of the thermometer, the signs and symptoms of potential AEs, and how and when to contact study staff. Education by study staff will also include proper study drug storage at home (Group 3).
19. Distribute wallet card with investigator contact information and post-study DHCM medical statement.
20. Distribute Dengue Memory Enhancement Card (DMEC) to subjects.

Cohort 2 Study Day 4 (on-site visit)

1. **Daily dosing only:** Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Days 2 and 3. Record time of meal on Study Day 4.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
3. Review DMEC.
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document AEs.
6. Review and document concomitant therapy.
7. Prior to study drug administration, collect ~3 mL of blood for PK analysis. Record time of blood sample.
8. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, and NS1) and serum protein analysis.
9. Prior to study drug administration, collect ~2.5 mL for host RNA assessments.
10. Prior to study drug administration, collect ~3 mL for A1AG assessment
11. Perform evaluation of the injection site.
12. **Daily dosing only:** Administer maintenance dose of the study drug, JNJ-64281802/placebo within 30 minutes of meal. Record time of administration.

Cohort 2 Study Day 6 (on-site visit)

1. **Daily dosing only:** Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Day 5 (at home). Record time of meal on Study Day 6.
2. Record vital signs (Systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
3. Review DMEC.
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document AEs.
6. Review and document concomitant therapy.
7. Perform evaluation of the injection site.
8. Prior to study drug administration, collect ~15 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, and NS1).
9. Prior to study drug administration, collect ~15.7 mL of blood for PT/PTT, CBC with differential, and chemistry panel.

10. **Daily dosing only:** Administer maintenance dose of the study drug, JNJ-64281802/placebo within 30 minutes of meal. Record time of administration.

Cohort 2 Study Day 8 (on-site visit)

1. **Daily dosing only:** Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Day 7. Record time of meal on Study Day 8.
2. **Weekly dosing only:** Standard meal within 30 minutes prior to drug intake. Record time of meal on Study Day 8.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Review DMEC.
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Prior to study drug administration, collect ~3 mL of blood for PK analysis. Record time of blood sample.
9. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, and NS1), serum proteins and viral genome sequencing.
10. Prior to study drug administration, collect ~30 mL of blood for cellular immunity (PBMC) analysis.
11. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
12. Prior to study drug administration, collect ~3 mL for A1AG assessment
13. **Daily dosing AND Weekly dosing:** Administer maintenance dose of the study drug, JNJ-64281802/placebo within 30 minutes of meal. Record time of administration.

Cohort 2 Study Day 11 (on-site visit)

1. **Daily dosing only:** Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Days 9 and 10. Record time of meal on Study Day 11.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
3. Review DMEC.
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document AEs.
6. Review and document concomitant therapy.
7. Prior to study drug administration, collect ~ 3 mL of blood for PK analysis. Record time of blood sample.
8. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, and NS1), humoral immunity (IgG and IgM), and viral genome sequencing.
9. Prior to study drug administration, collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.
10. Prior to study drug administration, collect ~3 mL for A1AG assessment

11. **Daily dosing only:** Administer maintenance dose of the study drug, JNJ-64281802/placebo within 30 minutes of meal. Record time of administration.

Cohort 2 Study Day 13 (on site visit)

1. **Daily dosing only:** Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Day 12. Record time of meal on Study Day 13.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
3. Review DMEC.
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document AEs.
6. Review and document concomitant therapy.
7. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), serum proteins and viral genome sequencing.
8. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.
9. **Daily dosing only:** Administer maintenance dose of the study drug, JNJ-64281802/placebo within 30 minutes of meal. Record time of administration.

Cohort 2 Study Day 15: See below procedures depending on Daily or Weekly Dosing

Daily Dosing (On-site Visit)

1. Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Day 14. Record time of meal on Study Day 15.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
3. Review DMEC.
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Review and document AEs.
6. Review and document concomitant therapy.
7. **Blood sample collection prior to study drug administration:**
    a. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
    b. Collect ~30 mL of blood for cellular immunity (PBMC)
    c. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), and viral genome sequencing.
8. Administer maintenance dose of the study drug, JNJ-64281802/placebo. Record time of administration.

Weekly Dosing (On-site Visit; Entire Day)

1. Standard meal within 30 minutes prior to drug intake. Record time of meal on Study Day 15.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after >5 minutes rest, and body temperature in the absence of antipyretic medication.

3. Perform 12 Lead ECG prior to dosing, *should be performed in supine position, after ≥5 minutes rest in supine position.*
4. Review DMEC.
5. Perform interin history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Blood sample collection prior to study drug administration:
    a. Obtain ~3 mL of blood for pre-dose PK analysis within the 2 hours prior to dosing with study drug. Record time of blood sample.
    b. Collect ~30 mL of blood for cellular immunity (PBMC)
    c. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), and viral genome sequencing.
    d. Collect ~3 mL for A1AG assessment
9. Administer maintenance dose of the study drug, JNJ-64281802/placebo. Record time of administration.
10. Blood sample collection after study drug administration:
    a. Collect ~3 mL of blood for PK analysis at +1 hour after study drug administration. Record sample collection time.
    b. Collect ~3 mL of blood for PK analysis at +2 hours after study drug administration. Record sample collection time.
    c. Collect ~3 mL of blood for PK analysis at +4 hours after study drug administration. Record sample collection time.
    d. Collect ~3 mL of blood for PK analysis at +8 hours after study drug administration. Record sample collection time.
    e. Collect ~3 mL of blood for PK analysis at +12 hour after study drug administration. Record sample collection time.

Cohort 2 Study Day 18 (on-site visit)

1. **Daily dosing only**: Standard meal within 30 minutes prior to drug intake. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Days 16 and 17 (at home). Record time of meal on Study day 18.
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
3. Review DMEC.
4. Perform interim history and focused physical exam (if indicated), concentrating on any acute
   complaints.
5. Review and document AEs.
6. Review and document concomitant therapy.
7. Prior to study drug administration, collect ~3 mL of blood for PK analysis. Record time of blood sample.
8. Prior to study drug administration, collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG, IgM), serum protein analysis and viral genome sequencing.
9. Prior to study drug administration, collect ~2.5 mL of blood for host RNA assessments.

10. Prior to study drug administration, collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.
11. Prior to study drug administration, collect ~3 mL for A1AG assessment
12. **Daily dosing only:** Administer maintenance dose of the study drug, JNJ-64281802/placebo. Record time of administration.

Cohort 2 Study Day 21: See below procedures depending on Daily or Weekly Dosing

Day 21: Weekly Dosing (On-site Visit)

1. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
2. Review DMEC.
3. Perform interim history and focused physical exam, concentrating on any acute complaints.
4. Review and document AEs.
5. Review and document concomitant therapy.
6. **Blood sample collection:**
    a. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
    b. Collect ~30 mL of blood for cellular immunity (PBMC)
    c. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), and viral genome sequencing.
7. For applicable persons of childbearing potential, perform β-HCG testing

Day 21: Daily Dosing (On-site Visit; Entire Day)

1. Standard meal within 30 minutes prior to drug intake. Record time of meal on Study Day 21. Record whether study drug, JNJ-64281802/placebo, was administered with food and within 30 minutes prior to drug intake on Study Days 19 and 20 (at home).
2. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after >5 minutes rest, and body temperature in the absence of antipyretic medication.
3. Perform 12 Lead ECG prior to dosing, *should be performed in supine position, after ≥5 minutes rest in supine position.*
4. Review DMEC
5. Perform interin history and focused physical exam, concentrating on any acute complaints.
6. Review and document AEs.
7. Review and document concomitant therapy.
8. Blood sample collection prior to study drug administration:
    a. Obtain ~3 mL of blood for pre-dose PK analysis within the 2 hours prior to dosing with study drug. Record time of blood sample.
    b. Collect ~30 mL of blood for cellular immunity (PBMC)
    c. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), humoral immunity (IgG & IgM), and viral genome sequencing.
    d. Collect ~3 mL for A1AG assessment
9. Administer maintenance dose of the study drug, JNJ-64281802/placebo. Record time of administration.
10. Blood sample collection after study drug administration:

a. Collect ~3 mL of blood for PK analysis at +1 hour after study drug administration. Record sample collection time.
b. Collect ~3 mL of blood for PK analysis at +2 hours after study drug administration. Record sample collection time.
c. Collect ~3 mL of blood for PK analysis at +4 hours after study drug administration. Record sample collection time.
d. Reassess vital signs at +8 hours post study drug administration. Collect ~3 mL of blood for PK analysis at +8 hours after study drug administration. Record sample collection time.
e. Collect ~3 mL of blood for PK analysis at +12 hour after study drug administration. Record sample collection time.

11. For applicable persons of childbearing potential, perform β-HCG testing

Cohort 2 Study Day 25 (+1/-1 days, on-site visit)

1. Review DMEC.
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam (if indicated), concentrating on any acute complaints.
6. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
7. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, qualitative PCR, plaque assay, NS1), and viral genome sequencing.
8. Collect ~3 mL for A1AG assessment

Cohort 2 Study Day 27 (+1/-1 days, on-site visit) – Visit to be conducted only if DENV-3 viral load positive on Day 25 in at least 1 participant of the group recruited on the same day or later.

1. Review DMEC.
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, qualitative PCR, plaque assay, NS1), and viral genome sequencing.

Cohort 2 Study Day 29 (+1/-1 days, on-site visit)

1. Review DMEC.
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam (if indicated), concentrating on any acute complaints.
6. For applicable persons of childbearing potential, perform β-HCG testing.

7. Review pregnancy prevention with the subject.
8. Collect ~30 mL of blood for PBMCs
9. Collect ~15 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG and IgM), and viral genome sequencing.
10. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
11. Collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.
12. Collect ~3 mL for A1AG assessment.

Cohort 2 Study Day 32 (+1/-1 days, on-site visit)

1. Review DMEC.
2. Review and document AEs.
3. Review and document concomitant therapy.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam (if indicated), concentrating on any acute complaints.
6. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, qualitative PCR, plaque assay, NS1), humoral immunity (IgG and IgM), and viral genome sequencing.

Cohort 2 Study Day 34 (+1/-1 days, on-site visit) – Visit to be conducted only if DENV-3 viral load positive on Day 32 in at least 1 participant of the group recruited on the same day or later.

1. Review and document AEs.
2. Review and document concomitant therapy.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform interim history and focused physical exam (if indicated), concentrating on any acute complaints.
5. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, qualitative PCR, plaque assay, NS1), humoral immunity (IgG and IgM), and viral genome sequencing.

Cohort 2 Study Day 36 (+2/-2 days, on-site visit)

1. Review and document AEs.
2. Review and document concomitant therapy.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform interim history and focused physical exam (if indicated), concentrating on any acute complaints.
5. Collect ~10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, and viral genome sequencing.

Cohort 2 Study Day 43 (+3/-3 days, on-site visit)

1. Review and document AEs
2. Review and document concomitant therapy.

3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Collect 10 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG & IgM and neutralizing antibody), serum proteins and viral genome sequencing.
6. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
7. Collect ~3 mL for A1AG assessment.

Cohort 2 Study Day 57 (+2/-2 days, on-site visit)

1. Review and document AEs.
2. Review and document concomitant therapy.
3. Review pregnancy prevention with the subject.
4. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
5. Perform interim history and focused physical exam, concentrating on any acute complaints.
6. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
7. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, and viral genome sequencing.
8. Collect ~10.7 mL of blood for PT/PTT, CBC with differential, and CMP.
9. Collect ~3 mL for A1AG assessment.

Cohort 2 Study Day 70 (+2/-2 days, on-site visit)

1. Review and document AEs.
2. Review and document concomitant therapy.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform interim history and focused physical exam, concentrating on any acute complaints.
5. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG, IgM), serum proteins and viral genome sequencing.
6. Collect ~3 mL for A1AG assessment.

Cohort 2 Study Day 85 (+3/-3 days, End of Study)

1. Review and document AEs.
2. Review and document concomitant therapy.
3. Record vital signs (systolic and diastolic blood pressure and pulse/heart rate supine after ≥ 5 minutes rest, and body temperature in the absence of antipyretic medication).
4. Perform 12-Lead ECG, *should be performed in supine position, after ≥5 minutes rest in supine position.*
5. Perform interim history, concentrating on any acute complaints.
6. Obtain weight.
7. Perform complete physical examination.
8. For applicable persons of childbearing potential, perform β-HCG testing.
9. Review pregnancy prevention with the subject.

10. Collect ~3 mL of blood for PK analysis. Record time of blood sample.
11. Collect ~20 mL of blood for DENV-3 viral load determination (quantitative PCR, plaque assay, NS1), qualitative PCR, humoral immunity (IgG, IgM, & neutralizing antibody), serum proteins and viral genome sequencing.
12. Collect ~30 mL of blood for cellular immunity (PBMC).
13. Collect ~2.5 mL of blood for host RNA assessments.
14. Collect ~3 mL for A1AG assessment.

7.18 Unanticipated Admission and Discharge Criteria

If a participant has a fever, they will be instructed to recheck their temperature in one hour per protocol. If fever persists, then participants will be asked to take acetaminophen, an antipyretic. If the participant remains febrile at one hour following medication, they will be asked to come to the clinic for evaluation. Clinical evaluation will consist of assessment by a clinician, physical exam, and laboratory evaluation (complete blood count, alanine aminotransferase [ALT], international normalized ratio [INR]/ partial thromboplastin time [PTT]). If the participant does not meet criteria for admission as below, then the participant will be allowed to go home and return to the clinic the next day for clinician evaluation. If the participant does meet criteria for admission as below, then the inpatient stay may range from 3-9 days (or longer) depending on clinical symptoms. Dosing with JNJ-64281802/placebo will continue unless specific pausing criteria are met.

Admission to the inpatient unit or hospital will ultimately be based on the investigator's discretion whether it is appropriate for the participant to be monitored in the inpatient unit versus sent to the emergency department for evaluation and treatment. Below are general guidelines for admission to the inpatient unit or hospital but the decision ultimately will be up to the investigator's discretion. If the volunteer is not ill enough to warrant admission the inpatient unit or hospital but does not feel well enough to come to the clinic for follow-up evaluation, a tele-health visit will be done.

Criteria for inpatient or hospital admission would include:

Body temperature >38.0°C (100.4 °F) for >12 hours with any one of the following:

- One Grade 3 value for absolute neutrophil count (ANC) per the modified US FDA Toxicity Grading Scale (Appendix 1: Modified US FDA Toxicity Grading Table); OR
- One Grade 3 value or two Grade 2 values for platelets, ALT, or INR/PTT per the modified US FDA Toxicity Grading Scale (Appendix 1: Modified US FDA Toxicity Grading Table); OR
- Clinical evidence of dehydration with inability to tolerate oral fluids; OR
- Clinician discretion.

The unit will be staffed 24 hours a day for the duration of the inpatient stay. A clinician will evaluate all subjects at least twice per day for the duration of the inpatient stay and will be available 24 hours a day for the duration of the inpatient stay should he/she be needed. During the inpatient stay, the scheduled activities from the Schedule of Procedures (Table 3 [Cohort 1] and Table 4 [Cohort 2]) will be continued if admitted to the inpatient unit and if the participant continues to consent. If a participant is admitted to the hospital the Schedule of Procedures will be paused. During the inpatient unit stay, the frequency of vital signs monitoring will increase to at least 3 times a day and additional clinical laboratory studies may be performed to follow-up on any clinical laboratory abnormalities that may

have developed during the inpatient stay. Additional diagnostic studies may be performed should the subject's clinical condition warrant (e.g., chest x-ray [CXR], ultrasound, and ECG). Should a subject leave the inpatient unit early every effort will be made to follow-up with the subject daily to monitor for signs/symptoms of illness.

The participants will be discharged from the inpatient unit when they meet ALL of the following discharge criteria:

- Afebrile for 48 hours.
- Any other continuing AEs (possibly, probably, or related) are ≤ Grade 2.
- Reliable clinical follow-up can be assured.

All participants discharged from the inpatient unit or hospital will fall back to the default schedule of daily visits to the outpatient clinical trial unit until last dosing day, if continuing on treatment, and thereafter at the specified time points during the follow-up phase.

7.19 Dengue Memory Enhancement Card (DMEC)

On Study Day 1, subjects will be provided a dengue memory enhancement card which is used as a memory aid to help volunteers report temperature to staff when they return at the follow-up visits. They will be given the card on their Day 1 visit and will be asked to record their temperature twice daily through and including Day 29 (on-site temperature readings may be used for the temperature recordings if volunteer already has a site visit and will have their temperatures taken on site). Staff will review the DMEC at each study visit through Study Day 29 and record the temperature on a separate source document.

The DMEC will not be collected by the study staff as subject's recordings will not be considered required data.

Staff will instruct subjects how to use the thermometers, to take their temperatures at approximately the same times each day, and to take additional temperatures if they feel they have elevated temperatures. Subjects will be asked to wait at least 15 minutes after eating, drinking, and smoking before taking their temperatures. They will be asked to confirm an elevated temperature (≥100.4°F) by retaking the temperature after a 20-minute interval and at 1 hour. Elevated temperatures not documented to last at least 1 hour will not be considered an AE or included in the analysis.

Following Day 29, temperature will only be recorded (outside of routine recordings at study visits) if the volunteer feels feverish.

7.20 Clinical Laboratory Testing

Using standard techniques, Quest Diagnostics, or other CLIA certified laboratories will perform the following tests:

1. CBC with differential
2. Chemistry panel
    - Sodium
    - Potassium

- Chloride
- Bicarbonate
- Blood urea nitrogen (BUN)
- Creatinine
- Glucose
- Calcium
- Phosphate
- Albumin
- Total protein
- Total cholesterol
- AST
- ALT
- Gamma-glutamyltransferase (GGT)
- Total bilirubin
- Alkaline phosphatase
- Uric acid
- High-density lipoprotein (HDL) cholesterol
- Low-density lipoprotein (LDL) cholesterol
- Triglycerides
- Magnesium (Cohort 1 only)
- Calculate creatinine clearance (by MDRD formula)
- Lipase
- Amylase

2. A1AG (Cohort 2 only)
3. PT/PTT
4. HIV assay (screening antibody assay with confirmation for positive antibody assays)
5. Hepatitis B screening by testing for Hepatitis B Surface Antigen (HBsAg)
6. Hepatitis C screening by testing for Hepatitis C antibody. If positive, test is confirmed by testing for Hepatitis C RNA. If Hepatitis C antibody is positive but RNA is negative, the volunteer is assessed as having a past infection that has been cleared. In this case, the subject is eligible for the study.
7. Urinalysis (in the event of an abnormal urine dipstick test)
8. Serum β-HCG, if required
9. Urine toxicology screen

In addition, clinic staff may perform an Alcohol Breath Test at the discretion of PI/provider using a commercially available kit.

Urine and serum β-HCG testing will be performed at the clinical trial site using an FDA-approved pregnancy test kit. Urine dipstick testing will be performed at the clinical trial site using an FDA-approved product. In the event of a reactive β-HCG test, a serum sample will be sent to the appropriate lab for confirmation. HIV testing may be performed at the clinical trial site using an FDA-approved rapid test kit or sent to the clinical laboratory. In the event of a reactive rapid HIV test, a serum sample will be sent to the appropriate lab for confirmation. Determination of DENV virus titer by RT-PCR and virus culture, plaque reduction neutralization antibody assays, antiviral activity assessments, pharmacokinetic concentrations, humoral immune response, biomarker assessments, viral genome sequencing, HLA genotyping and pharmacogenomic evaluations and cellular immune studies will be done either at the clinical trial site laboratory or at the DDT's indicated site laboratory.

7.21 Medical History and Concomitant Medications

Participants must have discontinued all medication, including over-the-counter products, herbal medication, or dietary supplements such as products containing *Hypericum perforatum* (St. John's wort) at least 7 days (Study Day -12 or longer, based on half-life) before first dose of study drug, **except** for vitamins, paracetamol/acetaminophen, anticoagulant medication, aspirin, or non-steroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy in postmenopausal female participants, and other select medications with restrictions listed below. Contraceptive medications should be continued and follow the requirements as listed in the inclusion/exclusion criteria.

The following medications other than the study drug are allowed during (a part of) the study:

- Vitamins

- Acetaminophen [TYLENOL] and ibuprofen [ADVIL or MOTRIN] may be used up to 3 days before first dose of study drug (Cohort 1 Day -8 and Cohort 2 Day -5). After that, the investigator may permit the use of acetaminophen/ibuprofen from 3 days before first dose of study drug until the last PK sample has been taken (Study Day 85) at ≤2000 mg per day, and ≤5 grams per week for acetaminophen and up to 1200 mg per day and <5 grams per week for Ibuprofen. In case acetaminophen/ibuprofen is used, the date and time of dosing, the indication, the dose, and the dosing regimen must be recorded in the Concomitant Therapy Section of the CRF. If possible, participants should avoid taking acetaminophen/ibuprofen within 6 hours before measuring body temperature.

- Occasional use of aspirin or NSAIDs [except for ibuprofen; see guidance above] is allowed at the discretion of the investigator and on a case-by-case discussion with Janssen. Aspirin can interfere with the ability of the blood to clot. It is not anticipated that any participants will have severe DENV infection with bleeding problems, however, it is still recommended to avoid these drugs. The investigator may recommend acetaminophen or an equivalent, which can be used safely for fevers and body aches. In case anticoagulant medication aspirin, or NSAIDs are used, the date and time of dosing, the indication, the dose, and the dosing regimen must be recorded in the Concomitant Therapy Section of the CRF.

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

- Certain other medications are allowed including metformin, levothyroxine, H_1 and H_2 receptor antagonists, weak CYP3A4 inhibitors, , selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitiors, tricylclic anti-depressants, anxioloytics, and benzodiazepines

Other comedication is allowed in the following cases:

- In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents in the recommended dose scheme is permitted.
- In case of severe nausea, the use of anti-emetics, except domperidone, is permitted.

In case any of these medications are used, the dose and dosing regimen must be recorded in the Concomitant Therapy Section of the CRF.

Participants must not receive investigational vaccines from 6 months before first dose of study drug until 90 days after last dose of study drug, licensed live attenuated vaccines from 28 days before first dose of study drug until 28 days after last dose of study drug, or other licensed (not live) vaccines from 14 days before first dose of study drug until 14 days after last dose of study drug. COVID-19 licensed or EUA vaccines are allowed to be received at any point during the study. Vaccinations against DENV and ZIKV are not allowed until 90 days after last dose of study drug. In case the participant is vaccinated, the dose must be recorded in the Concomitant Therapy Section of the CRF.

Participants must not use any immunosuppressive corticosteroids (excluding topical and nasal) or immunosuppressive drugs from 28 days before first dose of study drug until 28 days after last dose of study drug. An immunosuppressive dose of corticosteroids is defined as $\geq$10 mg prednisone equivalent per day for $\geq$14 days. In case immunosuppressive corticosteroids or immunosuppressive drugs are used, the date and time of dosing, the indication, the dose, and the dosing regimen must be recorded in the Concomitant Therapy Section of the CRF.

Participants must not use any strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole) [weak CYP3A4 inhibitors are allowed], CYP3A4 inducers (eg, phenytoin, rifampin), or substrates for CYP3A4 with a narrow therapeutic range (eg, alfentanil, cyclosporin), UGT1A9 inhibitors or inducers (eg, probenecid, rifampin, mefenamic acid), CYP2C8 (eg, repaglinide), CYP2C9 (eg, warfarin, tolbutamide), BCRP (eg, Pravastatin and folic acid), or CYP2C19 (eg, S-mephenytoin, omeprazole) from 14 days before first dose of study drug until 28 days after last dose of study drug. In case any of these inhibitors or substrates are used, the date and time of dosing, the indication, the dose, and the dosing regimen must be recorded in the Concomitant Therapy Section of the CRF.

If medical conditions not related to the study arise after inoculation and dictate the use of medications, participants are encouraged to obtain appropriate care, comply with the course of therapy as prescribed by their physician, and inform the investigator as soon as possible. The DDT must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition (relative to the moment of signed ICF), the condition must be documented in the Adverse Event Section of the CRF.

Concomitant therapies must be recorded in the CRF throughout the study from the screening visit performed between Days -12 and -6 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. If a volunteer is screened but not subsequently enrolled, concomitant therapy will not be followed from the time the participant is deemed ineligible or enrollment is complete without the subject receiving the test article.

7.22 Retention of Study Subjects

We will employ several strategies aimed at retaining subjects through study completion. During screening, we will obtain detailed primary locator information, as well as secondary contact information. Subjects will also provide information for people who may be contacted if primary and secondary means of contact fail. Locator information will be reviewed with subjects at each visit (i.e., addresses, phone numbers, email addresses). In addition, birthday cards/holiday cards may be mailed to check addresses, and reminders may be sent using various methods (including but not limited to phone, email, text messaging, electronic media, and postal mail). All data will be maintained and updated in a password protected locator database.

8 Adverse Event Monitoring

8.1 Definitions

8.1.1 Adverse Event

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

All AEs will be evaluated for severity, action taken, seriousness, outcome and relationship to either/both test articles as described in section 8 in this protocol.

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE. AEs will be collected for the duration of the study beginning study specific consenting and any test article-related AEs identified throughout the study period will be followed until resolution. If a subject consents but is not subsequently enrolled, AEs for that subject will not be followed from the time the subject is deemed ineligible for enrollment or enrollment is complete without the subject receiving the test article.

AEs are categorized as solicited AEs and other AEs. Solicited AEs include local reactogenicity, systemic reactogenicity, and laboratory events. Solicited AEs are those events that the clinician is specifically evaluating are listed in Table 13. All AEs are evaluated using the Adverse Event Grading Table in 13.1, Appendix 1.

All abnormal laboratory findings will be reviewed on a routine basis by the PI to identify potential safety signals. An abnormal lab not included on the toxicity table should be assessed in a similar fashion to the criteria above.

8.1.2 Adverse Reaction

An adverse reaction is an AE that is caused by an investigational agent (drug or biologic).

8.1.3 Suspected Adverse Reaction (SAR)

An AE for which there is a reasonable possibility that the investigational agent caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the test article and the AE. A suspected adverse reaction (SAR) implies a lesser degree of certainty about causality than adverse reaction that implied a high degree of certainty.

Table 13: Solicited Adverse Events

Systemic Reactogenicity	Local Reactogenicity
-Fever	-Injection site pain
-Headache	-Injection site erythema
-Retro-orbital pain (ROP)	-Injection site tenderness
-Nausea	-Injection site induration
-Fatigue	-Injection site pruritis
-Myalgia	
-Arthralgia	
-Drug Rash	
-Rash Maculo-Papular	
-Loss of Appetite	
-Vomiting	
-Diarrhea	
-Abdominal Pain	

8.1.4 Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be serious adverse events (SAEs). Events that meet SAE criteria during pregnancy, delivery, or in the neonate (e.g., congenital anomaly/birth defect) are reportable to the Clinical Safety Office (CSO) per the sponsor's reporting guidelines. Pertinent obstetrical information for all pregnancies will be reported to the CSO via the REDCap reporting system within 1 business day from site awareness of the pregnancy on the Pregnancy Notification and Outcome Form.

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site's awareness on a protocol-specified form.

If a volunteer becomes pregnant, she will not be included in the per protocol analysis but will be included in the intent-to-treat (ITT) analysis

- The pregnancy will be reported to the DSMB and/or IRB (if applicable).
- The pregnancy will be reported to Janssen Drug Development Team.

8.1.5 Serious Adverse Event (SAE)

An SAE is an AE that is determined to be "serious" whether considered related to the investigational agent or not. SAEs will be collected for the duration of the trial. An SAE results in 1 or more of the following outcomes:

- Death during the period of protocol-defined surveillance (enrollment through study discharge).
- Life threatening event, defined as an event that places a subject at immediate risk of death at the time of the event and does not refer to an event that hypothetically might have caused death were it more severe.
- Inpatient hospitalization or prolongation of existing hospitalization, defined as at least an overnight stay in the hospital or emergency ward for treatment that would have been inappropriate if administered in the outpatient setting.
- Congenital anomaly or birth defect.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Other medically important event*.

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

Each AE will be classified by the investigator/designee as "serious" or "non-serious." A SAE needs to meet only 1 or more of the above criteria to be considered serious.

8.1.6 Unexpected Adverse Events

An AE is considered unexpected if it is not listed in the IB or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. "Expected" does not mean that the event is expected with pharmacologically similar drugs, the underlying disease(s) or concomitant medications. It is the responsibility of the IND Sponsor to make this determination.

8.1.7 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

A SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

8.1.8 Unanticipated Problem

An Unanticipated Problem (UP) is any event, incident, experience, or outcome that is:

1. unexpected in terms of nature, severity, or frequency in relation to
    a. the research risks that are described in the IRB-approved research protocol and informed consent document; IB or other study documents; and
    b. the characteristics of the subject population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (An AE with a serious outcome will be considered increased risk).

8.1.9 Unanticipated Problem that is not an Adverse Event (UPnonAE)

An unanticipated problem that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

8.1.10 Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy, or reliability of the study data. Protocol deviations are designated as serious or non-serious and further characterized as:

1. Those that occur because a member of the research team deviates from the protocol
2. Those that are identified before they occur but cannot be prevented
3. Those that are discovered after they occur

8.1.11 Serious Protocol Deviation

A serious protocol deviation is any change, divergence, or departure from the study design or procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy, or reliability of the study data.

8.1.12 Non-compliance

The failure to comply with applicable NIH Human Research Protection Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to subjects
    b. Decreases potential benefits to subjects
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing

8.1.13 Pre-Existing Conditions, Worsening of Pre-existing Condition

Stable chronic conditions which are present prior to study specific consenting and do not worsen are not considered AEs and will be accounted for in the subject's medical history. Exacerbation or worsening of pre-existing conditions are defined as AEs and are evaluated using the same criteria described in section 8.2 in this protocol.

8.2 Assessment of Adverse Events

8.2.1 Identification of Adverse Events

All AEs occurring from the time the subject signs study specific consent through the end of the study will be documented, recorded, and reported. If the subject signs the consent but is not subsequently enrolled, AEs will no longer be collected from the time the subject is deemed ineligible for enrollment or enrollment is complete without the subject receiving test article. The Investigator will assess all AEs

with respect to Seriousness, Severity, and Causality according to the following guidelines. An assessment of safety will include clinical observations and monitoring of hematological, blood chemistry, and immunologic parameters. Safety will be evaluated by monitoring the subjects for local and systemic adverse reactions during the course of the trial.

Cohort 1: Subjects will be closely monitored for 30 minutes following administration of study agent(s) at in person visits until Day 3 of dosing. Subjects will be seen in the clinic nearly every other day between Study Days -6 and 29. An overnight admission to the inpatient unit will occur on Study Days -6 to -4 for a period of intensive PK sampling. Additionally, subjects will return to the clinic on Study Days 36, 43, 50, 57, 63, 70 and 85 at a minimum, and may be asked to return more often if warranted. Telephone visits will occur on Study Days -3, -2, 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, and 20 to gather relevant study information and assess for AEs.

Cohort 2: Subjects will be closely monitored for 30 minutes following administration of study agent(s) at in person visits until Day 1 of dosing. Subjects will be seen in the clinic every 2-3 days between discharge from the inpatient unit and Study Day 21. An overnight admission to the inpatient unit will occur on Study Days -3 to 1 for a period of intensive PK sampling. Additionally, subjects will return to the clinic every 3-4 days between Study Day 25 and Study Day 36; and every 1 to 2 weeks thereafter until Study Day 85. If a participant tests positive for DENV-3 RNA on Study Day 25 (or Study Day 21 if 25 is not available), additional visit on Day 27 and Day 34 should occur meaning 2-3 days sampling is required. Outpatient study visits will occur on Study Days 4, 6, 8, 11, 13, 15, 18, 21, 25, 29, 32, 36, 43, 57, 70, and 85 at a minimum, and participants may be asked to return more often if warranted.

Study staff will review subjects' reported temperatures and/or clinical temperatures from Study Day 1 through Study Day 29 to assess for AEs. At each visit through Study Day 29, subjects will be queried about possible study drug/challenge-related AEs (solicited AEs) and will have a focused physical exam performed excluding Cohort 1 Day -6 and Cohort 2 Day -3. A study clinician will be available to subjects by telephone or pager 24 hours a day during the study evaluation period.

All AEs will be recorded (e.g., in the study-specified case report form [CRF]/research database) through the duration of the study, unless as stated above the subject signs consent but is not subsequently enrolled.

All SAEs will be assessed appropriately as AEs and reported following SAE reporting guidelines outlined in section 8.3.2 of this protocol.

8.2.2 Protocol-Specific Adverse Event Definitions

Fever: Temperature ≥ 100.4°F lasting at least 1 hour.
Drug Rash: Drug induced exanthem; a cutaneous reaction to a drug typically characterized by hives, and/or blisters, and/or erythema, consistent with drug rash.
Rash Maculo-Papular: Areas of macular or maculo-papular rash over the trunk and/or extremities and may include the face/neck area as well, similar to dengue like rash seen in previous dengue challenge studies.
Headache: A pain located in the head, over the eyes, at the temples, or at the base of the skull.
ROP: Bilateral pain situated behind the orbits of the eye.
Nausea: Discomfort in the stomach with an urge to vomit.
Fatigue: Excessive tiredness following minimal exertion.

Myalgia: Pain in the muscles that is found in > 2 muscle groups.
Arthralgia: Pain that is found in > 2 joints.
Loss of Appetite: Decreased desire to eat, unintentional weight loss and not feeling hungry.
Vomiting: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Diarrhea: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.
Abdominal pain: A disorder characterized by a sensation of marked discomfort in the abdominal region, lasting at least several minutes.

8.2.3 Determination of Severity

The investigator/designee will assess all AE severity using the following classifications.

Table 14: Severity Definitions

Severity	Defined
Grade 1 (Mild)	Event that is easily tolerated, may require 1 dose of medication/treatment
Grade 2 (Moderate)	Event that interferes with daily activity or requires more than 1 dose of medication/treatment
Grade 3 (Severe)	Event that prevents daily activity and requires medical intervention
Grade 4 (Life-threatening)	An AE that is deemed by the study clinician, the medical monitor, or an outside clinician caring for the subject to be a life-threatening event
Grade 5 (Death)	Any AE that results in the death of the subject

Solicited AE severity grading classifications are listed in Table 15. All other AEs will be graded in severity using the Adverse Event Grading Table in Appendix 1: Modified US FDA Toxicity Grading Table.

Table 15: Local and Solicited Adverse Events

Local Reactogenicity	Grade	Severity
Injection Site Tenderness Injection Site Pruritis Injection Site Pain	1	Event that is easily tolerated, may require 1 dose of medication
	2	Event that interferes with daily activity or requires > 1 dose of medication
	3	Event that prevents daily activity
	4	Life-threatening
Injection Site Induration Injection Site Erythema	1	>0 - 20 mm
	2	>20 - 50 mm
	3	>50 mm
	4	Life threatening
Systemic Reactogenicity	**Grade**	**Severity**
Fever (oral)	1	100.4° F – 101.4°F
	2	101.5°F – 102.4°F
	3	≥102.5°F
	4	Life-threatening
Rash Maculo-Papular	1	Rash is present but asymptomatic and may require one dose of medication.
	2	Rash is symptomatic (pruritus/pain), and/or requires more than one dose of medication but does not interfere with function.
	3	Rash is symptomatic and interferes with function
	4	Life-threatening

Drug Rash	1	Rash is present but asymptomatic and may require one dose of medication.
	2	Rash is symptomatic (pruritus/pain), and/or requires more than one dose of medication but does not interfere with function.
	3	Rash is symptomatic and interferes with function
	4	Life-threatening
Headache Retro-orbital pain Nausea Fatigue Myalgia Arthralgia Abdominal Pain	1	Event that is easily tolerated, may require 1 dose of medication/treatment
	2	Event that interferes with daily activity or requires more than 1 dose of medication/treatment
	3	Event that prevents daily activity
	4	Life-threatening
Loss of Appetite	1	Loss of appetite without alteration in eating habits
	2	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated
	3	Associated with significant weight loss or malnutrition (e.g. inadequate oral caloric intake and/or fluid intake); tube feeding or TPN indicated
	4	Life threatening consequences; urgent intervention indicated
Vomiting	1	Intervention not indicated
	2	Outpatient IV hydration; medical intervention indicated
	3	Tube feeding, TPN or hospitalization indicated
	4	ER visit or hospitalization for hypotensive shock
Diarrhea	1	Increase of <4 stools per day over baseline
	2	Increase of 4-6 stools per day over baseline
	3	Increase of 7 or more stools per day over baseline; hospitalization indicated; limiting self care ADL
	4	ER visit or hospitalization
Dengue-specific laboratory parameters	**Grade**	**Severity**
Hemoglobin (Women)	1	9.5–10.7 gm/dL
	2	8.0–9.4 gm/dL
	3	< 7.9 gm/dL
	4	Life-threatening
Hemoglobin (Men)	1	11–12.5 gm/dL
	2	9.0–10.9 gm/dL
	3	< 8.9 gm/dL
	4	Life-threatening
Neutropenia (Reduced ANC)	1	750–999/mm^3
	2	500–749/mm^3
	3	< 500 mm^3
	4	Life-threatening
Leukocytosis (Increased WBCs)	1	11,500–13,000/mm^3
	2	13,001–15,000/mm^3
	3	≥ 15,000 or < 1,000/mm^3
	4	Life-threatening
Thrombocytopenia (Decreased Platelets)	1	≥ 100,000–120,000/mm^3
	2	≥ 75,000–99,999/mm^3
	3	< 74,999/mm^3
	4	Life-threatening
PT	1	> 1.0–1.25 x ULN
	2	> 1.25–1.5 x ULN
	3	> 1.5 x ULN
	4	Life-threatening
PTT	1	> 1.0–1.66 x ULN
	2	> 1.66–2.33 x ULN

	3	> 2.33 x ULN
	4	Life-threatening
ALT	1	> 1.25–2.5 x ULN
	2	> 2.5–5.0 x ULN
	3	> 5.0 xULN
	4	Life-threatening

8.2.4 Relationship with Receipt of JNJ-64281802 Test Article or Challenge

The clinical investigator will assess all AEs for their relationship to the JNJ-64281802 test article or challenge using the following classifications:

Definitely related:	Clear-cut temporal association, with no other possible cause
Probably related:	Reasonable temporal association, and a potential alternative etiology is not apparent
Possibly related:	Less clear temporal association; other etiologies also possible
Unlikely related:	Temporal association between the AE and the JNJ-64281802 test article /challenge, or the nature of the event is such that the JNJ-64281802 test article/challenge is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible)
Unrelated:	The AE is completely independent of JNJ-64281802 test article/challenge administration, and/or evidence exists that the event is definitely related to another etiology

The degree of certainty with which an AE can be attributed to study agent administration will be determined by how well the event can be understood in terms of one or more of the following:

- A reaction of a similar nature having previously been observed with this type of JNJ-64281802 test article or challenge, and/or formulation or naturally occurring dengue illness
- The event having often been reported in the literature for similar types of test articles or challenge products

All local injection-site reactions will be considered causally related to inoculation. Causality assessment is based on information available at the time of the AE assessment. The investigator may revise the causality assessment as additional information becomes available.

8.2.5 Adverse Event Action Taken

The investigator/designee will assess the action taken by the subject or the study staff in relation to the AE, using the following classifications:

Action

1 = None
2 = Remedial therapy (more than 1 dose of medication required)
3 = Discontinued study
4 = Hospitalization
5 = Other

8.2.6 Adverse Event Outcome

The investigator/designee will assess the outcome of the AE, either at resolution or the end of the study period, using the following classifications:

Outcome
1 = Resolved
2 = Continuing
3 = Continuing Chronic Condition
4 = Unknown, Off-Study before could confirm resolution of AE
5 = Death
6 = Unknown

8.2.7 Adverse Event Seriousness

The investigator/designee will categorize all AEs as either serious or non-serious using the criteria defined in section 8.2.3 of this protocol.

Any events defined as serious will also be reported following SAE reporting guidelines outlined in section 8.3.2 of this protocol.

8.3 Adverse Event Reporting

8.3.1 Non-Serious Adverse Events

Non-serious AEs will be followed to resolution or until the study ends and will be reported to the sponsor and DDT as requested, to the IRB according to IRB policies, to the DSMB as required, and to the FDA at least annually in the annual report. If a volunteer signs consent but is not subsequently enrolled the AE will not be followed to resolution or reported.

AEs meeting the pausing criteria outlined in section 8.5 of this protocol will be reported to the sponsor and DDT following the SAE reporting guidelines. AE data will be submitted to the IND Sponsor and DDT when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

8.3.2 Serious Adverse Events

Office of Clinical Research Policy and Regulatory Operations Clinical Safety Office (OCRPRO) and Janssen Drug Development Team (DDT)

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported according to the sponsor's reporting plan by using the REDCap system. Deaths and immediately life threatening SAEs must be reported to the CSO and the Janssen DDT within 1 business day after the site becomes aware of the event. All other SAEs will be reported within 3 working days of notification of the SAE occurrence to:

- REDCap website: https://crimsonredcap.cc.nih.gov/redcap/index.php
- OCRPRO CSO Phone: 301-846-5301, Fax: 301-846-6224, E-mail: rchspsafety@mail.nih.gov
- Janssen Drug Development Team Email: IIS-BIO-VIRO-GCO@its.jnj.com

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g., the subject is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator on the AE CRF and according to the sponsor's reporting guidelines.

SAEs that occur after the study follow-up period (Study Day 85) that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

SAEs that occur after the subject signs consent but prior to enrollment, will not be followed until resolution and will not be reported.

Data and Safety Monitoring Board
All SAEs must be reported by telephone (followed by written report), email, or fax within 1 working day of notification of the SAE occurrence to:

- The DSMB executive secretary – Phone: 301-846-5301, Fax: 301-846-6224, Email: niaiddsmbia@mail.nih.gov

Johns Hopkins University Biosafety Committee
All SAEs must be reported by telephone (followed by written report), email, or fax within 1 working day of notification of the SAE occurrence to:

- The JHU Institutional Biosafety Committee: Phone: 410-955-5918, Fax 410-955-5929

Institutional Review Board Reporting
All SAEs will be reported to Western Copernicus Group Institutional Review Board (WCG IRB) and JHSPH IRB as per guidelines below:

- WCG IRB Guidelines:
  - WCG IRB Phone: 855-818-2289
  - www.WCGIRB.com for updated reporting guidelines
- JHSPH IRB Guidelines:
  - JHSPH IRB Phone: 1-888-262-3242, Fax: 410-502-0584
  - https://www.jhsph.edu/offices-and-services/institutional-review-board/index.html for updated reporting guidelines

8.3.3 Unanticipated Problems

Unanticipated Problems that are also AEs must be reported to the CSO and sent by using the REDCap system no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the Sponsor CSO.

Report UPs that are also AEs to the CSO according to the sponsor's reporting guidelines or a local IRB UP form.

UPs that occur after the subject signs consent the subject but does not subsequently get enrolled will not be followed to completion and will not be reported.

8.4 Sponsor's Reporting Responsibilities

SUSARs, as defined in 21 Code of Federal Regulations (CFR) 312.32 and determined by the IND sponsor, must be reported to the FDA and all participating investigators as IND Safety Reports.

The sponsor will also submit a brief report of the progress of the investigation to the FDA on an annual basis, as defined in 21 CFR 312.33.S

AEs that are also unanticipated problems will be summarized by the IND sponsor and distributed to investigators.

8.5 Pausing Rules for the Study

The pausing criteria for both JNJ-64281802 and rDEN3Δ30 are listed below. The pausing criteria for individual subjects in this study include any one or more of the following:

- A subject experiences an SAE that is unexpected (per the investigator's brochure or product label) and possibly, probably, or definitely related to a study agent;
- A subject experiences two grade 3 or greater AEs that are unexpected (per the investigator's brochure or product label) and possibly, probably, or definitely related to a study agent.

The principal investigator/study chair(s) or the CSO may also pause dosing/study interventions for one or more subjects for any safety issue. The study safety oversight bodies (e.g., DSMB, SMC, and/or ISM) may recommend a pause to the CSO.

8.5.1 Reporting a Pause

If a pausing criterion is met, a description of the AE(s) or safety issue must be reported by the principal investigator within 1 business day to the CSO and the IRB according to their requirements. The principal investigator will also notify the DSMB. In addition, if applicable the CSO or designee will notify all other site investigators by email or through the specified pathway.

8.5.2 Resumption Following a Pause

The CSO, in collaboration with the principal investigator, DSMB, and the Janssen Drug Development Team (and/or DDUT if applicable) will determine if study activities, including both JNJ-64281802 and rDEN3Δ30 administration, may be resumed and any additional modifications or requirements that may apply, for the affected subject(s), or whether the events that triggered the pause require expansion to a study halt (see below).

The CSO or sponsor designee will notify the principal investigator of the decision. The principal investigator will notify other investigators and the IRB of the decision according to the IRB's process.

8.5.3 Discontinuation of Study Agent

A subject who does not resume study agent/intervention/treatment will continue to be followed for protocol-specified safety assessments or as clinically indicated, whichever is more conservative.

8.6 Halting Rules for the Study

The halting criteria for both JNJ-64281802 and rDEN3Δ30 are listed below. If during the study, dosing with JNJ-64281802 or rDEN3Δ30 is considered to raise significant safety concerns (i.e., when a specific set of halting criteria have been met), further dosing of participants will be halted pending a review of all available data by the study sponsor (OCRPRO), the NIAID Intramural DSMB, the site and the Janssen Drug Development Team (and/or DDUT if applicable) to assess whether the halt can be lifted or not, or whether other steps are needed.

8.6.1 Halting rules for JNJ-64281802

Below is a list of events that will lead to a halt in further dosing with study drug and an emergency DSMB meeting called for the Board to consider whether to lift the study halt. Unless indicated otherwise, the list is only applicable for concerned AEs that are considered related to study drug by the investigator. If safety concerns in Cohort 1 would only raise at the highest dose, further dosing of

participants at the highest dose will be halted while randomization and dosing at the lower dose levels may continue. The randomization ratio to JNJ-64281802 versus placebo will be kept at the 2:2:1 ratio.

- ≥2 participants in a cohort have ≥ Grade 3 rash events, regardless of study drug relatedness; OR
- ≥2 participants in a cohort have ≥1 JNJ-64281802-related SAE; OR
- ≥6 participants in a cohort have ≥ Grade 3 JNJ-64281802-related AEs independent of within or not within the same system organ class; OR
- ≥6 participants in a cohort have ≥ Grade 2, JNJ-64281802 related laboratory abnormalities that are considered clinically relevant by the investigator.

8.6.2 Halting rules for rDEN3Δ30

As rDEN3Δ30 is a challenge virus and is expected to have greater reactogenicity than a vaccine or therapeutic, different halting criteria will be used following administration of this virus. Following administration of rDEN3Δ30, the following criteria will be used to define unacceptable reactogenicity of the challenge virus.

1. One or more subjects in a cohort experience an SAE (as defined in section 8.1.5 of this protocol) that is determined to be possibly, probably, or definitely related to rDEN3Δ30 (as defined in section 8.2.4 of this protocol);
2. One or more subjects in a cohort experience anaphylaxis that is possibly, probably, or definitely related rDEN3Δ30;
3. Three or more subjects in a cohort experience the same Grade 3 laboratory abnormality that is possibly, probably, or definitely related to rDEN3Δ30;
4. Three or more subjects in a cohort experience an ANC < 500/mm^3 for any duration[1]; or
5. Three or more subjects in a cohort experience a dengue-like illness following rDEN3Δ30 administration, defined as an infection[2] associated with fever and two of the following symptoms:
    a. Grade 3 or greater headache lasting ≥ 48 hours
    b. Grade 3 or greater generalized myalgia lasting ≥ 48 hours

[1]These halting rules resulted from previous discussions between NIAID and the FDA on Phase 1 clinical trials of similar investigational live attenuated DENV vaccines (reference INDs 8463, 13730, and 13886) and dengue controlled human infection model viruses (reference INDs 15753 and 16765).

[2]Infection is defined as recovery of dengue virus by culture or PCR from the blood of a volunteer

8.6.3 Reporting a Study Halt

If a halting rule is identified by the Study PI/Protocol Chair and/or the CSO, a description of the AE(s) or safety issue will be reported by the PI or designee within 1 business day of sponsor awareness to the other Site Investigators. The Study PI/Protocol Chair will notify the DSMB and the Janssen Drug Development Team. The Site Investigators will notify their local IRBs. Safety data reports and changes in study status will be submitted to the applicable IRB promptly, in accordance with institutional policy. This constitutes a minimum criterion, and the decision to halt the trial may be made on the basis of any other criteria that, in the judgment of the investigators, FDA, IRB, DSMB, DDT (and/or DDUT if applicable) or Sponsor, indicate a potentially serious safety concern.

8.6.4 Resumption of a Halted Study

The CSO, the NIAID Intramural DSMB, and the Janssen Drug Development Team (and/or DDUT if applicable) will assess whether the halt can be lifted or not, or whether other steps are needed. The

CSO or designee will notify the site investigators of the decision to resume the study. The site investigators will notify their local IRB(s) of the decision.

8.7 Safety Oversight

8.7.1 Safety Review and Communications Plan and Transfer of Regulatory Obligations

A Safety Review and Communications Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the IND Sponsor CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

The IND Sponsor and the PI will sign a formal Safety Review and Communication Plan (SRCP) which documents that the PI has accepted the responsibility for periodic safety surveillance assessments as outlined in 21 CFR 312.32(b).

8.7.2 Sponsor Medical Monitor

A Medical Monitor representing the IND Sponsor (OCRPRO), will be appointed for oversight of safety in this clinical study. The Sponsor Medical Monitor will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan (SRCP) as defined in section 8.7.1

8.7.3 NIAID Intramural Data and Safety Monitoring Board

The NIAID intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The NIAID intramural DSMB is constituted to review the safety data of NIAID intramural clinical studies that require DSMB oversight, and consists of experts in infectious diseases, biostatistics, and clinical trials. The PI's designee will provide the DSMB executive secretary with blinding codes in a sealed envelope in case the DSMB requires this information to make its recommendations. The DSMB will review the study prior to initiation and twice a year thereafter. The board may convene additional reviews as necessary. Prior to each review, the PI will submit a summary of cumulative safety data in a format acceptable (by unblinded cohort if requested) to the board. The board will review the study data to evaluate the safety, efficacy, study progress and conduct of the study. Reports of SAEs will be submitted by the PI to the board at the same time they are reported to the sponsor and IRB. All unanticipated problems will be submitted to the DSMB at the same time they are submitted to the IRB or IND sponsor. IND Safety Reports will be submitted to the DSMB by the investigator after their receipt. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI will notify the board at the time halting criteria are met, and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB(s).

9 Statistical Consideration

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

9.1 Sample Size Determination

Cohort 1 is intended to assess CCI [redacted] of the superior antiviral activity of the highest dose of JNJ-64281802 when compared to placebo and to collect data for the characterization of a relationship between the PK and antiviral activity of JNJ-64281802 based on DENV-3 RNA.

A higher number of participants will be randomized to the highest dose group to get a better estimate on the effect on DENV-3 RNA at the highest feasible dose.

Based on the currently available data, the infection rate under placebo is assumed to be 90% and the mean log_{10} AUCD1-D29 (VL) of those participants who are infected is assumed to be 5.5 log_{10} copies/mL/28 days with an STD of 0.70 log_{10} copies/mL/28 days.

These data were used to simulate 10,000 trials, each with 6 participants on placebo and 10 participants on high dose, or a total of 16 participants. Data were simulated using a Bernoulli distribution for the infection rate. For those participants who were infected, the corresponding log_{10} AUCD1-D29 (VL) was simulated using a normal distribution. Under the hypothesis that active study drug is superior to placebo at the highest dose, the mean of the normal distribution for participants on active study drug was reduced with 30% for the high dose, while the same SD was used over the different groups. To be able to draw valid conclusions on the antiviral activity of JNJ-64281802, at least 65% of the inoculated placebo participants should test positive for DENV-3. With the assumed infection rate of 90%, the probability of model failure (i.e., <65% of inoculated placebo participants infected) is <2%. The results over the 10,000 simulated trials are shown in Table 16.

Table 16: Mean (STD) Log_{10} AUCD1-D29 (VL) (Log_{10} Copies/mL/28 Days) in Infected Participants per Study Drug in 10,000 Simulations

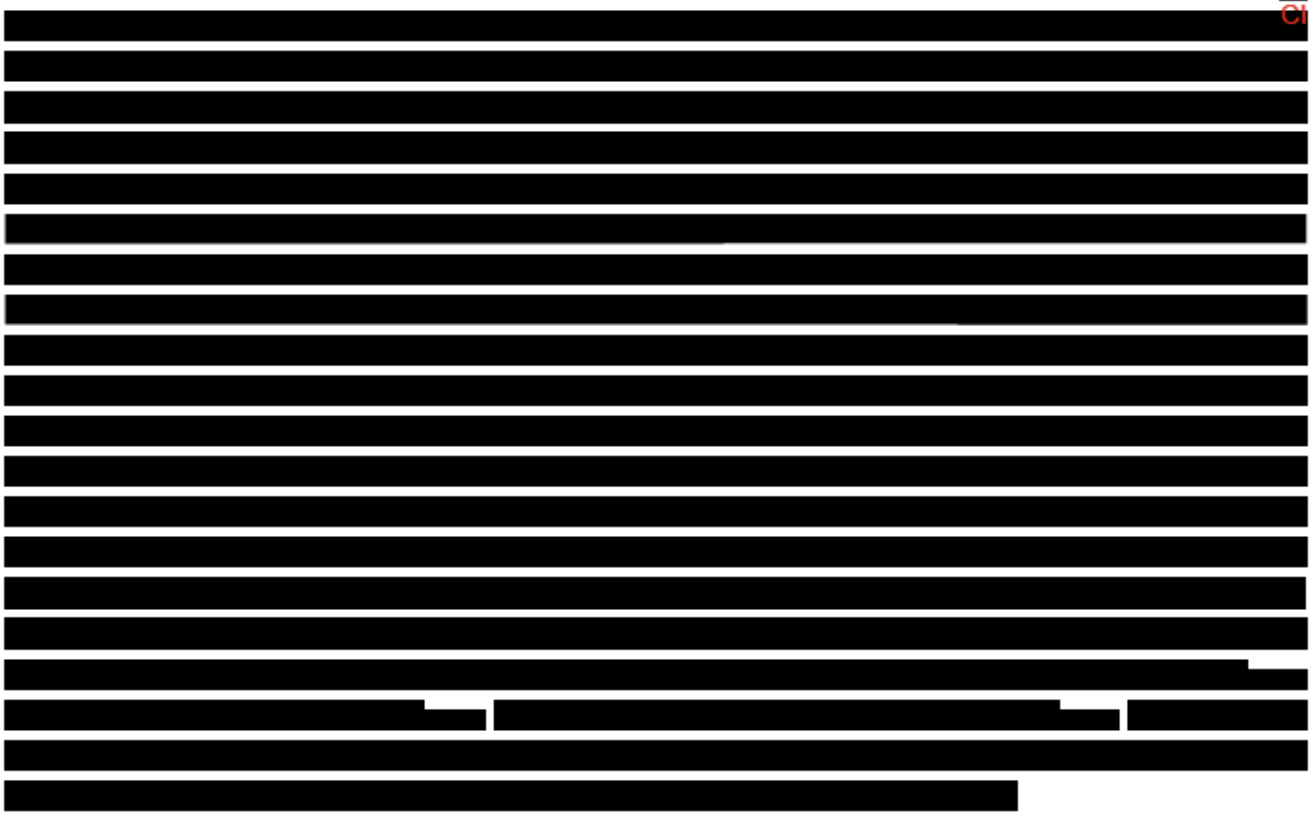
	Placebo	JNJ-64281802
		High
Mean	5.50	4.05
STD	0.66	0.53

Note: Table presents the means of the 10,000 means and standard deviations. Simulated values below 3.1 log_{10} copies/mL/28 days were considered as noninfected participants. The median infection rate was 78% in the high dose group and 100% placebo dose group.

A tobit analysis was done in each of the simulated trials for which at least 65% of inoculated placebo participants were infected, with the log10 AUCD1-D29 (VL) as dependent variable and treatment as a fixed covariate. In this analysis of variance model for left-censored data, a normally distributed error term was used. Values are left censored at the value 3.1 log_{10} copies/mL/28 days, with 40 copies/mL the assumed limit of detection. CCI [redacted] The number of participants in Cohort 1 is considered sufficient for the initial characterization of a relationship between the PK and antiviral activity of JNJ-64281802. In order to account for a potential early discontinuation of a maximum of 7 participants can be replaced in case of discontinuation before last dose of study drug on Day 21.

Based on the interim analysis results of Cohort 1, up to 3 dosing regimens (dose, dosing duration, and dosing frequency) can be selected for evaluation in Cohort 2 (section 9.5). Cohort 2 is intended to further characterize the antiviral activity of JNJ-64281802 and the relationship between the PK and the antiviral activity based on DENV-3 RNA. Within Cohort 2, an additional 24 participants can be randomized in an equally balanced ratio (1:1:1 in case of 3 groups) to the selected JNJ-64281802 dosing regimens and matching placebos. . In order to account for a potential early discontinuation rate of up to 25%, a maximum of 6 participants can be replaced in case of discontinuation before Day 21 .

The selection of the mid and low dose in addition to the high dose is to support the objective to characterize the relationship between the exposure of JNJ-64281802 and the antiviral activity of JNJ-64281802. To this end, a population modeling approach will be used, based on a viral kinetic model previously developed to describe the viremia-time profile during a primary Dengue infection [19]. C



The total sample size for the study will be a maximum of 67 participants over the 2 cohorts, ie, 4 participants for the High-dose Sentinel Group (Group 1a), 12 participants for Group 1b, 14 participants for Group 2, 7 possible replacements for Cohort 1, 24 participants for Cohort 2, and 6 possible replacements for Cohort 2.

9.2 Antiviral Activity Analyses

All participants who are randomized, who are inoculated with the recombinant DENV-3, and who receive at least 1 dose of study drug will constitute the ITT population. All participants who are included in the ITT population without protocol deviations that affect the antiviral activity assessment will constitute the per-protocol (PP) population. The PP population will be used for all antiviral activity analyses to test the prophylactic effect under optimal conditions. Treatment assignment for this population will be defined by actual treatment received. As sensitivity analysis, the ITT population will also be used in an exploratory analysis. Note that subsequent confirmatory trials in the field will use the ITT population for analysis to assess the activity of the drug in terms of real-world feasibility. Treatment assignment for this population will be defined as treatment planned by randomization.

The antiviral activity analyses will only be valid in case at least 65% of the inoculated participants in the placebo group test positive for DENV-3 (ie, have detectable DENV-3 RNA), otherwise no antiviral activity conclusions can be drawn from this study.

9.2.1 Primary Endpoint

The primary analysis will be based on a tobit ANOVA analysis with $\log_{10}$ $AUC_{D1\text{-}D29}$ (VL) as dependent variable and treatment as a fixed covariate. As for the determination of the sample size (section 9.1), a normally distributed error term will be used. Values will be left censored at the value 2.70 $\log_{10}$ copies/mL/28 days, with 36 copies/mL the assumed limit of detection and values <LOD imputed with 18 copies/mL

CCI [redacted]

CCI [redacted].

Descriptive statistics on the area under the time DENV-3 RNA curves will be calculated for each group separately.

9.2.2 Secondary Endpoints

The primary analysis will be repeated with $AUC_{D1\text{-}D29}$ ($\log_{10}$VL) as dependent variable. Values will be left censored at the value 35.28 $\log_{10}$ copies/mL/28 days, with 36 copies/mL the assumed limit of detection and values <LOD imputed with 18 copies/mL

Descriptive statistics and mean (and standard error (SE)) graphs will be shown of the $\log_{10}$ DENV-3 RNA actual values and changes from baseline over time.

The proportion of participants within the DENV-3 RNA categories (≥ lower limit of quantification [LLOQ], < LLOQ target detected and < LLOQ target not detected) will be shown in a frequency tabulation per analysis time point.

Time to first onset of detectable DENV-3 RNA will be analyzed using Kaplan-Meier estimates analysis. 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% confidence intervals based on log-log transformation method, will be presented. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by treatment.

The peak DENV-3 RNA and the duration of detectable DENV-3 RNA will be analysed using descriptive statistics.

Similar analyses will be performed for the DENV-3 viremia.

Frequency tabulations and descriptive statistics will be used to summarize the occurrence and duration of DENV infection-associated AEs.

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

Descriptive statistics will be provided per Cohort and dose regimen. Placebo data will be pooled by Cohort, over the different regimens.

9.3 Safety Analysis

All safety analyses will be made on the Safety population. All participants enrolled into the study who receive at least 1 dose of study drug will be included in the safety population. Participants in this population will be defined by the study drug received, not by randomization assignment.

Safety data will be presented descriptively by Cohort. No statistical testing of safety data is planned. Baseline will be defined as the last observation before first dose of study drug for all safety analyses.

9.3.1 Adverse Events

The verbatim terms used in the CRF by the investigator to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after first dose of study drug through the day of last dose plus 20 days is considered to be treatment emergent. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study drug group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study drug due to an AE, or who experience an AE of at least Grade 3, or an SAE.

The modified US FDA Toxicity Grading Table in Appendix 1: Modified US FDA Toxicity Grading Table will be used for AE reporting in this study.

9.3.2 Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results (Grade 3 or Grade 4) will also be provided.

9.3.3 Vital Signs

Vital signs including body temperature, pulse/heart rate and blood pressure (systolic and diastolic) (supine) will be summarized over time, graphically and/or using descriptive statistics. The percentage of participants with values beyond clinically important limits (see Appendix 1: Modified US FDA Toxicity Grading Table) will be summarized.

9.3.4 Physical Examinations

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

9.4 Electrocardiogram Assessments

The effects on cardiovascular variables (safety ECGs) will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values to allow detection of clinically relevant changes in individuals. The ECG variables that

will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB), QT corrected according to Fridericia's formula (QTcF). Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds to ≤ 60 milliseconds, or >60 milliseconds. The percentage of subjects with abnormalities and treatment-emergent abnormalities will be tabulated.

9.5 Pharmacokinetic Analysis

All participants who received at least 1 dose of study drug and who have at least 1 PK parameter value will be included in the PK analysis. All participants who received at least 1 dose of study drug and who have at least 1 plasma concentration data value after dosing will be included in the descriptive statistics.

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

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

Cohort 1: Predose plasma concentrations (C_{trough}) on Days -4, 1, 7, 9, 11, 16 and 21 will be compared graphically to assess the achievement of steady-state concentrations of JNJ-64281802.

Cohort 2 Daily Dosing: Predose plasma concentrations (C_{trough}) on Days -1, 1, 4, 8, 11, 15, 18, and 21 will be compared graphically to assess the achievement of steady-state concentrations of JNJ-64281802.

Cohort 2 Weekly Dosing: Predose plasma concentrations (C_{trough}) on Days -1, 1, 8, and 15 will be compared graphically to assess the achievement of steady-state concentrations of JNJ-64281802.

Special attention will be paid to the plasma concentrations and PK parameters of those participants who died, who have discontinued the study due to an AE, or who experienced an AE of at least Grade 3, or an SAE.

9.6 Immune Analyses

9.6.1 Humoral Immune Analyses

Seroconversion will be defined as a ≥ 4-fold increase in dengue antibody titer (IgM, IgG, or neutralizing Ab) at any time-point post-DENV-3 challenge compared with baseline.

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

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

9.6.2 Cellular Immune Analyses

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

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

9.6.3 Biomarkers Analyses

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

9.6.4 Pharmacokinetic/Pharmacodynamic Analyses

The relationship between the PK and antiviral activity of JNJ-64281802 will be explored graphically and analyzed using statistical methods, as data allow. A snapshot date for PK and PD samples to be analyzed will be defined, if required. Samples collected before this date will be included in the PK/PD analyses. Samples collected after the snapshot date will be analyzed at a later date and may be included in a PK/PD re-analysis when they become available after the subjects in Cohort 1 have completed or discontinued the study and the data have been cleaned. More details will be provided in a separate analysis plan and the results will be presented in a separate report.

Unblinded PK/PD analyses will be performed by independent internal pharmacometricians of Janssen using data available at a pre-defined snapshot date, with adequate firewalls so the DDT and study sponsor will remain blinded. At the time of the second interim analysis, the DSMB and DDUT will review results of the PK/PD analyses and the dosing regimen selected by the DDT.

If conducted, analysis results of the relationship between the PK and selected safety endpoints will be presented in a separate report.

9.6.5 Viral Genome Sequence Analyses

The results of DENV-3 viral genome sequencing will be evaluated by the sponsor virologist. Relevant changes in the DENV-3 viral genome will be tabulated and described for participants with detectable DENV-3 RNA during the study period.

Additional exploratory characterization of the DENV-3 viral genome sequence and phenotype may be performed and reported separately.

9.6.6 Human Leukocyte Antigen Typing and Pharmacogenomic Analyses

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

DNA samples will be analyzed for HLA genotyping and pharmacogenomic analyses. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

DNA samples may be used for research related to JNJ-64281802 and comedications, if applicable, or dengue. They may also be used to develop tests/assays related to JNJ-64281802 and comedications in the protocol, if applicable, and dengue. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to JNJ-64281802 and comedications, if applicable, or dengue clinical endpoints.

9.6.7 IgE Induced Myeloid Cell Degradation Analysis

Serum samples for in vivo research (to investigate potential JNJ-64281802-specific IgE induced myeloid cell degranulation) will be analyzed in participants who develop rash during the study. Samples will be collected from all participants predose at Day -5 (Cohort 1), Day -2 (Cohort 2), and prechallenge at Day 1. In participants who develop rash, the sample will be repeated when the rash is observed.

9.6.8 Interim Analysis

Two interim analyses are planned during the execution of the trial. The Board will review the interim analyses and decide whether the criterion of futility had been met.

Interim analysis #1 is planned as soon as the last participant in Group 1b completes Study Day 29 or discontinued earlier) and data entry is complete. This analysis will be CCI [redacted] considered as the primary analysis. The data for Groups 1a and 1b of Cohort 1 will be unblinded only for subjects included in this interim analysis and only for members of the DSMB, the DDUT and the DDT (see

Table 11: Summary of Schedule of Interim Analyses and Unblinding of Data

). Unblinding will occur after all the subjects in Groups 1a and 1b have completed Day 29 or discontinued earlier and the data have been cleaned. Enrolment can continue during this interim analysis execution. If the DSMB requests individual unblinded data prior to the interim analyses, it will be provided to them The results of this interim analysis will be shared with the study sponsor, the NIAID Intramural DSMB, the Janssen Drug Development Unblinded Team (DDUT), and the Janssen Drug Development Team (DDT). The study team will remain blinded for this analysis. The DSMB will review the interim analysis and make recommendations to continue or to stop the enrolment of Group 2, Cohort 1. CCI [redacted]. The Janssen DDT and DDUT will also review the interim analysis and make recommendations to proceed or not to proceed to Group 2, Cohort 1.The final decision to continue or stop the study will be taken in collaboration with the sponsor (OCRPRO), DDT, DDUT and DSMB. The trial may be stopped for futility based on the results of this analysis. The study team can get access to the unblinded results of this analysis when all subjects in Cohort 1, Group 1 (Groups 1a, 1b) have completed Study Day 85.

Interim analysis #2 is planned as soon as the last participant in Cohort 1 completes the trial (Study Day 85). As for the first interim analysis, data entry should be complete, and data should be fully cleaned before the code is broken. This interim analysis will be used to evaluate the relationship between the PK and antiviral activity of JNJ64281802, to determine whether additional dosing regimens will be evaluated in Cohort 2, and (if applicable) to decide on the dose, dosing durations, and dosing frequency for Cohort 2. The primary analysis will be repeated as a sensitivity analysis. The study sponsor will consult with the NIAID Intramural DSMB, and the Janssen Drug Development Team who analyzes and defines the dosing regimen(s) for Cohort 2. The DSMB will review the interim analysis and make recommendations to proceed or not to proceed with enrolment of Cohort 2. The Janssen DDT and DDUT will also review the interim analysis and make recommendations to continue or to stop the enrolment of Cohort 2.

For each of the interim analyses, aggregate data on DENV infection-associated AEs (rash included), data on primary and secondary endpoints, and PK data will be available for review, as appropriate, by the study sponsor, the NIAID Intramural DSMB, and the Janssen Drug Development Team to assess whether the study needs to continue. An expedited safety report will be prepared if the analysis indicates that these DENV infection-associated AEs occur more frequently in JNJ-64281802 recipients than in placebo recipients, suggesting that there may be a reasonable possibility of drug causality. The NIAID Intramural DSMB members, study team members, NIH statistician, the members of the Janssen DDT will be unblinded after all subjects in Cohort 1, Group 1 (Groups 1a, 1b) have completed Study Day 85. After enrolment of Cohort 1, Group 2, the NIAID Intramural DSMB members, study team members, NIH statistician, the members of the Janssen DDT will be unblinded after all subjects in Cohort 1, Group 2 have completed Study Day 85 and the database has been cleaned and closed. The SAP will describe the planned interim analyses in greater detail.

Reviews of safety data at times other than the times of interim analyses will be done by the DSMB with no unblinding of study team members or Janssen.

10 Data Collection and Monitoring

10.1 Source Documentation and Data Collection

Complete source documentation (laboratory test reports, hospital or medical records, progress notes, observations, etc.) is required for every study subject for the duration of the study. The subject's study record must record his/her participation in the clinical trial and, after unblinding, the randomization inoculation received (with doses and frequency) or other concomitant medications or interventions administered, as well as any adverse reactions experienced during the trial.

Data from source documentation for subjects enrolled in the study will be entered into the Clinical Research Information Management System of the NIAID (CRIMSON) Data System. The data entry is to be completed on an ongoing basis during the study. Data entry into CRIMSON will be performed by authorized individuals and each individual entering data into CRIMSON will have a unique user ID and password. Corrections to the data system shall be tracked electronically (password protected) with time, date, individual making the correction, and what was changed.

Corrections to the source document must be made by striking through the incorrect entry with a single line (taking care not to obliterate or render the original entry illegible) and entering the correct information adjacent to the incorrect entry. Corrections must be initialed and dated by the person making the correction whenever possible. Source documentation should support the data collected in CRIMSON **and** must be signed and dated by the person recording and/or reviewing the data.

The investigator is responsible for the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRIMSON Data System. All data entered into CRIMSON should be reviewed by the investigator/designee and signed as required with written or electronic signature, as appropriate. Data reported in CRIMSON should be consistent with source documents or the discrepancies should be explained. Source documentation will be made available for review or audit by the Sponsor or designee and any applicable Federal authorities.

10.2 Study Documentation

Study-related documentation will be completed as required by the IRBs, the Sponsor, and regulatory authorities. Continuing review documentation will be submitted by the investigator to the IRBs by the anniversary date of initial review as specified by each IRB. An annual report will be submitted by the Sponsor to the FDA according to regulations. These reports will provide a brief description of the progress of the investigation as outlined in the Code of Federal Regulations (CFR), Title 21, Part 312.33 (21 CFR 312.33), and will include any revisions of the protocol if not previously submitted.

The PI will maintain adequate records to account for the disposition of the investigational product, including dates of receipt and quantity, current inventory, and dispensation to subjects. If the study is terminated, suspended, or completed, all unused challenge virus will be disposed of per sponsor's instructions and unused JNJ-64281802 study product will be disposed of per DDT instructions.

10.3 Retention of Specimens

All specimens collected as part of this trial will be stored indefinitely for future research as part of our approved biosample repository for vaccine research. These samples may be used by the sponsor, the site, the Janssen drug development team or its partners to learn more about flavivirus infection and other diseases, or to understand JNJ-64281802 or develop tests related to JNJ-64281802. These samples will not be sold or used to make commercial products. All samples stored in the repository will be labeled with the study subject ID numbers, which, by themselves, cannot identify study subjects, but are linkable to other research databases (e.g., from questionnaires, clinical assessments, logbooks, etc.) generated by the main study. The repository database will contain only the study subject

ID numbers. A master log linking the study subject ID numbers to the names of the subjects will be maintained in a password-protected database system with limited access to authorized research team members.

Participants may withdraw their consent for their samples to be stored for future research.

10.4 Retention of Records

The PI is responsible for retaining all essential documents listed in the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Trial-related documents will be maintained by the investigator in a secure storage facility for a period of 2 years after final marketing approval or if 2 years have elapsed since the formal discontinuation of the product's clinical development. These records are also to be maintained in compliance with IRB, state, and federal medical records' retention requirements, whichever is longest. The sponsor is required to inform the investigator as to when such documents need no longer be retained. Storage of all trial-related documents will be such that confidentiality will be strictly maintained to the extent provided by federal, state, and local laws.

It is the PI's responsibility to retain copies of source documents until receipt of written notification to the contrary from NIAID OCRPRO. Study documents should not be destroyed without prior written agreement between NIAID OCRPRO and the PI. Should the PI wish to assign the study records to another party and/or move to another location, the PI must provide written notification of such intent to NIAID OCRPRO, with the name of the person who will accept responsibility for the transferred records and/or the new location. NIAID must be notified in writing, and written permission must be received by the site prior to destruction or relocation of research records.

10.5 Protocol Compliance

The PI will conduct the trial in compliance with the protocol agreed to by the sponsor. The investigator will not implement any deviation from, or changes to, the protocol without agreement, prior review, and documented approval by the sponsor, the DDT and the IRB that granted original approval for the study. The DSMB will be made aware of all protocol revisions (other than administrative) and will review any changes to the protocol that involve DSMB oversight or involve changes to the study's data and safety monitoring plan. However, the investigator may implement a deviation from, or change in, the protocol to eliminate an immediate hazard(s) to subjects without prior IRB or sponsor approval, or when the change(s) involves only logistical or administrative aspects of the trial (i.e., change of telephone number[s]). In the event of a medical emergency, the PI will perform any medical procedures that are deemed medically appropriate.

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Sponsor, DDT, IRB, DSMB, and the regulatory authorities.

10.6 Clinical Investigator's Brochure

Investigators will receive the current versions of the Clinical IBs for JNJ-64281802 test article and for rDEN3Δ30, which comprehensively describe all the available preclinical experience with the experimental JNJ-64281802 test article and challenge virus. If relevant new information becomes available during the course of the trial, the investigators will receive a revised brochure or an amendment to the current version.

10.7 Study Monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." The sponsor will monitor all aspects of the study, with respect to current GCP, for compliance with applicable government regulations. Prior to the start of the study, the investigator will be informed of the frequency of monitoring visits and will be given reasonable notification prior to each visit. The objectives of a monitoring visit will be to verify the prompt and accurate recording of all monitored data points, and prompt reporting of SAEs; to check the availability of signed informed consent forms and documentation of the informed consent process for each monitored subject; to compare CRIMSON reports and line listings with source data for completeness and accuracy; and to help ensure investigators are in compliance with the protocol. The monitors will also inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections, FDA) and applicable guidelines (ICH GCP) are being followed. During the monitoring visit, the investigator (and/or designee) and other study personnel should be available to discuss the study. Study documents must be available for review throughout the course of the study. The sponsor will retain original copies of Form FDA 1572 and copies of other study documents as deemed necessary.

The investigator (and/or designee) will make study documents (e.g., consent forms, CRIMSON, and pertinent hospital or clinical records) readily available for inspection by the local IRB, the FDA, the site monitors, and NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

11 Protection of Human Subjects

11.1 Institutional Review Boards

The PI will be responsible for obtaining IRB approval for the study. Before the start of the study, the appropriate documents (including, but not limited to, the protocol, IB, Informed Consent Form, information sheets, and advertisements) will be submitted to the IRB for approval. A copy of the study approval (including approval of the informed consent form) is to be maintained in the investigator study document binder and a copy will be supplied to the sponsor. During the study, the investigator is responsible for providing the IRB with all documents subject to review (e.g., protocol amendments, informed consent form updates, advertisements, and any written information that may be provided to the subject). Annual reports on the progress of the study will be made to the IRB by the investigator in accordance with IRB guidelines and government regulations.

11.2 Informed Consent

In obtaining and documenting informed consent, the investigator and study staff must comply with the applicable regulatory requirements, GCP guidelines, and ethical principles. The written informed consent form must be approved by the IRB prior to its use. The subject may withdraw consent at any time during the course of the trial. A copy of the informed consent document will be given to the subject for his or her records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.3 Risks

Risks to the subjects are associated with venipuncture, topical anesthetic cream, and study agent(s). These risks are outlined below. Female subjects will be cautioned of the unknown risk of study agents to the fetus and will be advised to use effective birth control methods for the duration of the study.

11.3.1 JNJ-64281802

JNJ-64281802 has been tested carefully and extensively in laboratory animals (rats and dogs) according to regulatory guidelines and it is considered generally safe and well tolerated in animals.

In clinical studies, during study 64281802DNG1001, when tested for the first time in healthy participants, JNJ-64281802 was generally safe and well tolerated. Two Grade 2 (mild to moderate) events of rash occurred in the multiple ascending dose part that were considered very likely related to JNJ-64281802 by the investigator. One Grade 2 (mild to moderate) rash occurred in a subject in the 10 day 560 mg JNJ-64281802 group, on the last day of dosing (Day 10), and resolved after 35 days. The other Grade 2 (mild to moderate) rash occurred in a subject in the 31-day 400 mg JNJ-64281802 group, on dosing Day 13, and resolved after 47 days. This subject completed the 31-day treatment period as planned. Based on this limited amount of data from FIH study 64281802DNG1001, rash is considered a potential risk. Careful clinical monitoring of rash events will be performed in all planned clinical studies for JNJ-64281802.

In female participants of childbearing potential, the effects of JNJ-64281802 on an unborn child or infant are not properly known. Precautions will be taken to prevent pregnancy in female subjects as outlined in section 5.1 above.

In male participants, the effect of JNJ-64281802 on an unborn child or infant are unknown. Taking the medicinal product during the study could lead to an unknown risk for an embryo or fetus and the effect of JNJ-64281802 on sperm is unknown. For this reason, barrier contraception is required as outlined in section 5.1 above.

Subjects may be asked to defer routine immunizations (such as influenza) until for 28 days prior to first dose of study drug and for 28 days following last dose of study drug for licensed live attenuated vaccines. Subjects may be asked to defer routine immunizations (such as influenza) until for 14 days prior to first dose of study drug and for 14 days following last dose of study drug for other licensed (not live) vaccines. The exception to this is COVID-19 vaccines licensed or under EUA. This may increase the risk that the subject will be infected with an influenza virus during this period. As with any investigational study agent, there is a theoretical possibility of risks about which we have no present knowledge. Subjects will be informed of any such risks should further information become available.

11.3.2 Challenge

Possible local challenge reactions include pain, swelling, or erythema for 2 to 3 days, lymphadenopathy, or pruritus at the injection site. Systemic reactions such as macular papular rash and transient neutropenia have been observed in some subjects infected with other recombinant dengue vaccine candidates. Other potential systemic reactions that may occur include symptoms of dengue such as fever, headache, photophobia, eye pain, rash, generalized myalgias, arthralgias, elevated ALT, neutropenia, elevated PTT, or decreased platelet count. Immediate hypersensitivity reactions including urticaria, anaphylaxis, or other IgE-mediated responses are possible, as with any product. Subjects who receive only rDEN3Δ30 may be at increased risk of more severe disease if they become infected with another wt DENV serotype in the future.

11.3.3 Venipuncture

The total amount of blood to be drawn throughout the 85-day duration of the study is approximately 678 mL for Cohort 1 and 610 mL for Cohort 2.

Risks occasionally associated with venipuncture include excessive bleeding, pain, bruising, or hematoma at the site of venipuncture, lightheadedness, and syncope (rarely). Infection may occur rarely

11.3.4 Peripheral Intravenous (IV) Catheter

Risks associated with peripheral IV catheter placement include excessive bleeding, pain, bruising, or hematoma at the site of IV placement. Lightheadedness or syncope (rarely). Air embolism, extravascular drug administration, and intraarterial injection are rare. Infection or inflammation may occur.

11.3.5 Topical Anesthetic Cream

Risks occasionally associated with the use of topical anesthetic cream include temporary skin discoloration, skin irritation, rash, hives, and rarely, dizziness or drowsiness.

11.4 Benefits

Subjects will not receive any direct benefit from participation in this study. They will receive a physical examination and laboratory screening for HIV infection, hepatitis B infection, and hepatitis C infection. They may potentially develop antibodies against one or more dengue viruses. It is hoped that information gained in this study will contribute to the development of a safe and effective treatment of dengue infection.

11.5 Compensation

Cohort 1: Subjects will be compensated up to $100 for screening, up to $200 for inoculation day (Day 1), up to $300 for each inpatient/full day (Day -6 and Day -5) and up to $250 for each full day (Day 21), up to $50 for at home dosing with phone call (Day -3, -2, 2, 4, 6, 8, 10, 12, 13, 15, 17, 19, 20), and up to $100 for each completed scheduled dosing or follow-up visit. They will also receive up to $75 for returning a completed temperature / dosing log. They will also receive up to a $300 bonus if all study visits are completed on time. Subjects will be compensated for the screening only if they are enrolled in the study. Subjects will only be compensated for the visits that they complete. Alternates who come to the clinic on Study Day -6 and are inpatient overnight but who are not dosed with study drug due to fulfillment of enrollment for that day will be compensated up to $200. Subjects enrolled in the study will receive a maximum total compensation of up to $4,175.

Cohort 2: Subjects will be compensated up to $200 for screening if enrolled, up to $250 for inoculation day (Day 1), up to $300 for each inpatient night (Day -3, -2, -1), and up to $250 for each full day (Day 15 for weekly dosing, and Day 21 for daily dosing), and up to $125 for each completed scheduled dosing or follow-up visit (17 total). They will also receive up to $75 for returning a completed temperature / dosing log. They will also receive up to a $300 bonus if all study visits are completed on time. Subjects will be compensated for the screening only if they are enrolled in the study. Subjects will only be compensated for the visits that they complete. Alternates who come to the clinic on Study Day -3 and are inpatient overnight but who are not dosed with study drug due to fulfillment of enrollment for that day will be compensated up to $200. Subjects enrolled in the study will receive a maximum total compensation of up to $3850 for standard follow up schedule consisting of 15 dosing or follow up visits ($4100 if Day 27 and Day 34 are indicated based on lab results)

11.6 Confidentiality

All study-related information will be stored securely at the study site. All subject information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, and process and administrative forms will be identified by coded number only to maintain subject confidentiality. Computer entry will be done using a study ID number for each subject and all local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointments books, and any other listings that link subject study ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. A subject's study information will not be released without the written permission of the subject, except as necessary for monitoring by the Sponsor and/or its contractors and the FDA.

11.7 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel during the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the NIH.

All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Please also refer to individual carrier guidelines (e.g., Federal Express, Airborne Express) for specific instructions.

12 Publication Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials' registration policy as a condition for publication. This policy requires that all clinical trials be registered prior to enrollment of any subject in a public trials registry, such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity, would be exempt from this policy.

13 Supporting Documentation

13.1 Appendix 1: Modified US FDA Toxicity Grading Table

General Severity Grading[1]	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV
Local Reactogenicity				
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Injection Site Pruritus	Pruritus that is easily tolerated	Pruritus that interferes with daily activity	Pruritus that prevents daily activity	Emergency room visit or hospitalization
Erythema/Redness	2.5 - 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling	2.5 - 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Systemic Reactogenicity	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Fever (Oral)	100.4° F – 101.4°F	101.5°F – 102.4°F	≥102.5° - 104°F	>104°F
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Retro-Orbital Pain (ROP)	No interference with activity	ROP that interferes with daily activity or requires >1 dose of medication	ROP that prevents daily activity	ER visit or hospitalization
Nausea	No interference with activity or 1 – 2 episodes in 24 hours	Interferes with daily activity or results in >2 episodes/24 hours	Prevents daily activity, requires outpatient hydration	ER visit or hospitalization
Fatigue	No interference with activity	Fatigue that interferes with daily activity or requires >1 dose of medication	Fatigue that prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Myalgia that interferes with daily activity or requires >1 dose of medication	Myalgia that prevents daily activity	ER visit or hospitalization
Arthralgia	No interference with activity	Arthralgia that interferes with daily activity or requires >1 dose of medication	Arthralgia that prevents daily activity	ER visit or hospitalization
Rash Maculo-Papular	Rash is present but asymptomatic, may require 1 dose of medication/treatment	Rash is symptomatic (pruritus/pain), interferes with daily activities or requires > 1 dose of medication	Rash is symptomatic and interferes with function	ER visit or hospitalization

General Severity Grading[1]	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV
Drug Rash (hives, blisters, erythema, consistent with drug rash)	Rash is present but asymptomatic, may require 1 dose of medication/treatment	Rash is symptomatic (pruritus/pain), interferes with daily activities or requires > 1 dose of medication	Rash is symptomatic and interferes with function	ER visit or hospitalization
Abdominal Pain	Abdominal pain that is present but easily tolerated, may require 1 dose of medication/treatment	Abdominal pain that interferes with daily activity or requires >1 dose of medication	Abdominal pain that prevents daily activity	ER visit or hospitalization
Loss of Appetite	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g. inadequate oral caloric intake and/or fluid intake); tube feeding or TPN indicated	ER visit or hospitalization
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN or hospitalization indicated	ER visit or hospitalization
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Solicited Lab AEs	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Hemoglobin (female)	9.5 - 10.7 gm/dL	8.0 - 9.4 gm/dL	≤7.9 gm/dL	ER visit or hospitalization
Hemoglobin (male)	11.0 - 12.5 gm/dL	9.0 – 10.9 gm/dL	≤8.9 gm/dL	ER visit or hospitalization
Neutropenia (Reduced ANC)[2]	≥750-999/mm3	≥500-749/mm3	≤500/mm3	ER visit or hospitalization
Leukocytosis (Increased WBCs)	11,500 - 13,000/mm3	13,001 - 15,000/mm3	≥15,000	ER visit or hospitalization
Thrombocytopenia (Reduced Platelets)	100,000 – 120,000/mm3	75,000 - 99,999/ mm3	≤74,999/mm3	ER visit or hospitalization
PT	>1.0 - 1.25 x upper limit of normal (ULN)	>1.25 - 1.5 x ULN	>1.5 x ULN	ER visit or hospitalization
PTT	>1.0 - 1.66 x ULN	>1.66 - 2.33 x ULN	>2.33 x ULN	ER visit or hospitalization
ALT (Alanine Aminotransferase)	>1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - <10 x ULN	> 10 x ULN
Other Laboratory Values	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Albumin, Low	3.0 to <LLN g/dL	≥2.0 to <3.0 g/dL	<2.0 g/dL	NA
Creatinine	1.5 - 1.7 mg/dL	>1.7 – 2.0 mg/dL	>2.0 - 2.5 mg/dL	> 2.5 or requires dialysis
Fibrinogen decrease – mg/dL	150 - 200mg	125 - 149	100 - 124	<100 mg/dL, or associated with gross bleeding, or associated

General Severity Grading[1]	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV
				with disseminated coagulation
Fibrinogen increase mg/dL	400 - 500	501 - 600	>600	--
Creatine phosphokinase (CPK)	≥1.5 x ULN- 2 x ULN	>2 x ULN- 4 x ULN	>4 - 10 x ULN	>10 x ULN
Sodium: Hyponatremia	130 – 134 mEq/L	123 – 129 mEq/L	<122 mEq/L	ER visit or hospitalization
Sodium: Hypernatremia	145 – 150 mEq/L	151 – 157 mEq/L	>158 mEq/L	ER visit or hospitalization
Potassium: Hypokalemia	3.1 – 3.2 mEq/L	2.9 – 3.0 mEq/L	<2.8 mEq/L	ER visit or hospitalization
Potassium: Hyperkalemia	5.2 – 5.5 mEq/L	5.6 – 6.0 mEq/L	>6.1 mEq/L	ER visit or hospitalization
Phosphate: Hypophosphatemia	2.0 – 2.2 mg/dL	1.5 – 1.9 mg/dL	<1.4 mg/dL	ER visit or hospitalization
Calcium (Corrected for Albumin): Hypocalcemia	1.95 – 2.04 mmol/L	1.75 – 1.94 mmol/L	<1.74 mmol/L	ER visit or hospitalization
Calcium (Corrected for Albumin): Hypercalcemia	2.51 – 2.88 mmol/L	2.89 – 3.13 mmol/L	>3.14 mmol/L	ER visit or hospitalization
Magnesium: Hypomagnesemia	0.60 – 0.74 mmol/L	0.45 – 0.59 mmol/L	<0.44 mmol/L	ER visit or hospitalization
Total Bilirubin (hyperbilirubinemia)	>1.1 to < 1.6 x ULN	>1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥5.0 x ULN
Glucose: Hypoglycemia (Nonfasting, No Prior Diabetes)	55 – 69 mg/dL	40 – 54 mg/dL	<39 mg/dL	ER visit or hospitalization
Glucose: Hyperglycemia (Nonfasting, No Prior Diabetes)	116 – 160 mg/dL	161 – 250 mg/dL	>251mg/dL	Insulin requirements or hyperosmolar coma
Bicarbonate, Low	16.0 to < LLN (mEq/L; mmol/L)	11.0 to < 16.0 (mEq/L; mmol/L)	8.0 to <11.0 (mEq/L; mmol/L)	<8.0 (mEq/L; mmol/L)
Cholesterol, Fasting, High	200 to <240 (mg/dL)	240 to <300 (mg/dL)	≥300 (mg/dL)	NA
LDL, Fasting, High	130 to <160 (mg/dL)	160 to <190 (mg/dL)	≥190 (mg/dL)	NA
Triglycerides	—	400 – 750 mg/dL	>751 mg/dL	
Liver Transaminase (LFTs) GGT AST Alk Phos	 >1.25 – 2.5 x ULN >1.25 – 2.5 x ULN >1.25 – 2.5 x ULN	 >2.5 – 5.0 x ULN >2.5 – 5.0 x ULN >2.5 – 5.0 x ULN	 >5.0 - 10x ULN >5.0 - 10x ULN >5.0 - 10x ULN	 >10x ULN >10x ULN >10x ULN
Pancreatic Amylase Lipase	>1.0 – 1.5 x ULN >1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN >1.5 – 2.0 x ULN	>2.0 - 5x ULN >2.0 - 5x ULN	>5x ULN >5x ULN
Uric Acid, High (mg/dL)	7.5 to <10.0 mg/dL	10.0 to <12.0 mg/dL	12.0 to <15.0 mg/dL	≥15.0 mg/dL
Other Cardiovascular	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted

General Severity Grading[1]	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV
Cardiac Arrhythmia	Asymptomatic; transient dysrhythmia, no therapy required	Recurrent/persistent dysrhythmia; symptomatic therapy required	unstable dysrhythmia, hospitalization and therapy required	ER visit or hospitalization for arrhythmia
Prolonged QTc Interval (as per Bazett's formula)	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g. Torsade de pointes, or other associated serious ventricular dysrhythmia)
Tachycardia – beats per minute	101 — 115	116 — 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute[3]	50 — 54	45 — 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension	Transient, increase >20 mm Hg diastolic BP; no therapy required	Recurrent; chronic increase >20 mm Hg diastolic BP; therapy req.	acute therapy required outpatient or hospitalization possible	ER visit or hospitalization for malignant hypertension
Hypotension	Transient orthostatic hypotension with heart rate increased by 20 beats/min or decreased by <10 mm Hg systolic BP, no therapy required	Symptoms or BP decreased by <20 mm Hg systolic, correctable with oral fluid therapy	Mean arterial pressure <60 mm Hg, IV fluids required, or hospitalization	ER visit or hospitalization for hypotensive shock
Pericarditis	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER or visit or hospitalization
Hemorrhage, Blood Loss	Minimal blood loss, asymptomatic, no therapy required	Symptomatic blood loss and no transfusion required	Symptomatic AND transfusion of 1-2 units of blood or packed red cells	Massive blood loss or > 2 units transfused
Other Gastrointestinal	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Oral Discomfort/Dysphagia	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids required	ER or visit or hospitalization
Constipation	Constipation less than 72 hours and requires medication for relief	Moderate abdominal pain 72 hours with impaction, requiring therapy	Requiring disimpaction or hospital treatment	ER or visit or hospitalization
Other Respiratory	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Bronchospasm Acute	Transient; no therapy; FEV1 or peak flow reduced to 70- <80%	Therapy required; normalizes with bronchodilator; FEV1 or peak flow 50 - 69%	No normalization with bronchodilator; FEV1 or peak flow 25 – 49%, retractions	ER or visit or hospitalization

General Severity Grading[1]	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	ER or visit or hospitalization
Other Neurologic	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Nuchal Rigidity	--	--	Presence of Nuchal rigidity	ER or visit or hospitalization
Neuropsychological	Mild confusion or cognitive impairment	Moderate confusion or cognitive impairment	Severe confusion or cognitive impairment	ER or visit or hospitalization
Neurocerebellar	Slight incoordination or dysdiadochokinesia	Intention tremor, dysmetria, slurred speech, or nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	ER or visit or hospitalization
Neuromotor	Mild weakness in muscle of feet, but able to walk; and/or mild increase in reflexes	Moderate weakness in feet or legs, e.g. unable to perform deep knee bend, mild weakness in hands, loss of previously present reflex or development of hyperreflexia.	Marked distal weakness	ER or visit or hospitalization
Neurosensory	Mild impairment (decreased sensation in focal area or symmetrical distribution)	Moderate symmetrical impairment, mild impairment that is not symmetrical	Severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple areas or functions	ER or visit or hospitalization
Paresthesia (Burning, Tingling, etc.)	Mild discomfort; no therapy required	Moderate discomfort; non-narcotic analgesia required	Severe discomfort; or narcotic analgesia required with symptomatic improvement	ER or visit or hospitalization
Other Dermatologic	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Dermatitis	Rash is present but asymptomatic	Rash is symptomatic (pruritus/pain) but does not interfere with function	Rash is symptomatic and interferes with function	ER or visit or hospitalization
Other Urinalysis	Grade I – Mild	Grade II – Moderate	Grade III – Severe	Grade IV- potentially life-threatening unless otherwise noted
Proteinuria: Random Urine	1+	2+ - 3+	4+	ER or visit or hospitalization
Proteinuria: 24 Hour Urine	200 mg – 1 g loss/day or <0.3% or <3 g/L	>1 – 2 g loss/day or 0.3% - 1.0% or 3 – 10 g/L	>2 g loss/day or >1.0% or >10 g/L	ER or visit or hospitalization
Hematuria (In the Absence of	Microscopic only, 6-10 rbc/hpf	>10 rbc/hpf	Gross, with or without clots;	ER or visit or hospitalization

General Severity Grading[1]	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV
Cervico-vaginal Bleeding)			or RBC casts	
Other Miscellaneous	Grade I – Mild	Grade II – Moderate	Grade III - Severe	Grade IV- potentially life-threatening unless otherwise noted
Malaise	Malaise that is easily tolerated	Malaise that interferes with daily activity	Malaise that prevents daily activity	ER or visit or hospitalization

1. Grade 5 will be assigned to any AE that results in death
2. These values for neutropenia are values that have been used in dengue controlled human infection model studies and dengue live attenuated vaccine studies
3. When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

13.2 Appendix 2: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in section 5.1, Inclusion Criteria.

Definitions

Persons of Childbearing Potential (POCBP)

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

Female Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in persons not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A person is considered postmenopausal definitively with > 24 months of consecutive amenorrhea and a FSH level is not required to confirm. If there is a question about menopausal status in persons on HRT, the person will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish to continue HRT during the study
- **permanently sterile** (for the purpose of this study)
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, and should have been performed ≥3 months before first dose of study drug.

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

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

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

Typical use failure rates may differ from those when used consistently and correctly.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine Device (Hormonal or Copper)
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Bilateral tubal occlusion
• Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the person of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 74 days.)
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug. c) Male condom and female condom should not be used together (due to risk of failure with friction).

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