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A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

Protocol VRC 705

Sponsored by
National Institute of Allergy and Infectious Diseases (NIAID)
Vaccine Research Center (VRC)
Bethesda, Maryland, USA

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Statement of Compliance

The trial will be conducted in compliance with the protocol, the applicable regulatory requirements including but not limited to the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR 46, 21 CFR including parts 50 and 56 concerning informed consent and Institutional Review Board (IRB)/Ethics Committee (EC) regulations, and 21 CFR 312 concerning Investigational New Drug (IND) application), International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidance, and the NIAID Clinical Terms of Contract Award. Each site will hold a current Federal Wide Assurance (FWA) issued by the Office for Human Research Protections for federally funded research. Completion of Protection of Human Subjects Training will be required for all study personnel in accordance with National Institutes of Health (NIH) policy.

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VRC 705: A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

Sponsored by:
Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)

I, the Principal Investigator for the indicated VRC 705 Study Site, agree to conduct this study in full accordance with the provisions of this protocol and protocol amendments. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation pertaining to the conduct of this study, including, but not limited to, case report forms, source documents, consent forms, laboratory test results, and medication inventory records, for at least 2 years following submission of a United States Biologics License Application. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. No study records will be destroyed without prior authorization from VRC/NIAID. Publication of the results of this study will be governed by the VRC/NIAID policies. Any presentation, abstract, or manuscript will be made available by the investigators to VRC Leadership and to NIAID for review prior to submission.

I have read and understand the information in this protocol and the Investigator's Brochure and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____	_____
Name/Title of Principal Investigator	Study Site Name/Identifier
_____	_____
Signature of Principal Investigator	Date

ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AoU	assessment of understanding
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CHIKV	chikungunya virus
CI	confidence interval
cm	centimeter
CMV	cytomegalovirus
CRO	contract research organization
DENV	dengue virus
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ELISA	enzyme-linked immunosorbent assay
ELISpot assay	enzyme-linked immunospot assay
EUA	emergency use authorization
FDA	United States Food and Drug Administration
GBS	Guillain-Barré syndrome
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
H0	null hypothesis
HF	hemorrhagic fever
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HTLV-1	Human T cell leukemia virus type 1
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IgM	immunoglobulin M
IM	intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
LAR	legally acceptable representative
MedDRA®	Medical Dictionary for Regulatory Activities

Abbreviation	Term
mITT	Modified intent-to-treat
NAb	neutralizing antibody
NHP	non-human primates
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NVITAL	NIAID Vaccine Immune T-Cell and Antibody Laboratory
PAHO	Pan American Health Organization
PBMC	peripheral blood mononuclear cells
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PDL	primary diagnostic laboratory
PI	Principal Investigator
PP	Per-protocol
prM	precursor for the M transmembrane protein
PRNT	plaque reduction neutralization test
PSRT	Protocol Safety Review Team
RBC	red blood cells
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
RVP	reporter virus particle
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SC	subcutaneous
SUSAR	serious and unexpected suspected adverse reactions
TBD	to be determined
ULN	upper limit of normal
UP	unanticipated problem
US	United States
VE	vaccine efficacy
VLP	virus-like particle
VP	Virus particles
VRC	Vaccine Research Center
WBC	white blood cell
WHO	World Health Organization
WNV	West Nile virus
WT	wild-type
ZIKV	Zika virus

DEFINITIONS

Term	Definition
Adolescents	15-17 years of age. Some countries may define adolescent age up to 21 years.
Endemic	Reported active local mosquito-borne transmission of ZIKV
Potential endemic	Active local mosquito-borne transmission of ZIKV may occur during the course of the study

PRÉCIS

Study Title: A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

Study Design: This is a multicenter, randomized study to evaluate safety, immunogenicity, and efficacy of a three-dose vaccination regimen with the Zika virus (ZIKV) wild-type (wt) DNA vaccine, VRC-ZKADNA090-00-VP, or placebo. The hypotheses are that the ZIKVwt DNA vaccine will be safe and will elicit a ZIKV-specific immune response. In **Part A**, the primary objective is to evaluate the safety and tolerability of the vaccine. In **Part B**, the primary objectives are to evaluate the safety and efficacy of the vaccine compared to placebo. Secondary and exploratory objectives of the study relate to immunogenicity and durability of immune responses.

Product Description: VRC-ZKADNA090-00-VP was developed by the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), and is composed of a single closed-circular DNA plasmid (VRC 5283) that encodes the wt precursor transmembrane M (prM) and envelope (E) proteins from the H/PF/2013 strain of ZIKV.

VRC-PBSPLA043-00-VP is sterile phosphate-buffered saline (PBS) prepared for human administration as a placebo.

Subjects: **Part A.** Healthy adults, 18-35 years of age, that reside in ZIKV endemic or potential endemic regions.
Part B. Healthy adults and adolescents, 15-35 years of age, that reside in ZIKV endemic or potential endemic regions. Study sites may choose to enroll adults and adolescents, or may opt to enroll only an adult population.

Study Plan: Subjects will receive study product intramuscularly (IM) in the limbs as specified by the group assignment. In **Part A,** 90 subjects will be randomized to vaccine at a 1:1:1 ratio to receive a 4 mg or 8 mg dose of vaccine split between 2 or 4 injections. In **Part B,** about 2400 subjects will be randomized to vaccine (4 mg) or placebo in a 1:1 ratio.

Vaccine safety and tolerability will be assessed by monitoring of clinical and laboratory parameters throughout the study. Solicited reactogenicity symptoms will be collected for 7 days after each product administration. The study schedule will include clinic visits with safety and immunogenicity blood samples collected at particular time points.

The vaccine dose and administration plan for **Part B** was selected based on **Part A** and Phase 1 data. Vaccine efficacy will be evaluated in **Part B** by comparing incidence of ZIKV cases between vaccine and placebo groups. During the study, when subjects exhibit any possible symptom of ZIKV infection, they will be evaluated by blood and urine ZIKV polymerase chain reaction (PCR). Stored blood and urine samples will also be assessed retrospectively by ZIKV PCR to identify possible asymptomatic cases. A Data and Safety Monitoring Board (DSMB) will oversee the study.

The product administration schema is as follows:

Part A							
Group	**Subjects**	**Total Dose**	**Number of Injections per Dose**	**Number of Limbs: Location of Injections**	**Administration Schema**		
					Day 0	**Week 4**	**Week 8**
1	30	4 mg	2	2 limbs: both arms	DNA	DNA	DNA
2	30	4 mg	4	4 limbs: both arms and legs	DNA	DNA	DNA
3	30	8 mg	4	4 limbs: both arms and legs	DNA	DNA	DNA
Total	**90***	Study product is administered IM by needle-free injection device.					
*Accrual up to a total of 100 subjects is permitted if additional subjects are needed for safety evaluations.							
Part B							
Group	**Subjects**	**Total Dose**	**Number of Injections per Dose**	**Number of Limbs: Location of Injections†**	**Administration Schema**		
					Day 0	**Week 4**	**Week 8**
4	1200	4 mg	2	2 arms	DNA	DNA	DNA
5	1200	0	2	2 arms	Placebo	Placebo	Placebo
Total	**2400**	Study product is administered IM by needle-free injection device.					
† Preferred location of injections is in both arms. Administration in the thighs may be allowed with IND Sponsor approval.							

Duration: **Part A**: Each subject will be followed for 32 weeks.
Part B: Each subject will be followed for 96 weeks.

1. INTRODUCTION

The Dale and Betty Bumpers Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), in Bethesda, Maryland, United States (US) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies to provide safe and effective means to prevent and control infectious diseases. Zika virus (ZIKV) is a mosquito-borne infection causing illness with mild symptoms including fever, rash, joint pain and conjunctivitis that may last for several days to weeks.

Since its discovery in Uganda in 1947, outbreaks of ZIKV have been reported in Africa, Southeast Asia, and the Pacific Islands. ZIKV emerged in Brazil in 2015 and then rapidly spread throughout the Americas [1]. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed ZIKV infection in Brazil and on February 1, 2016, the World Health Organization (WHO) declared ZIKV a public health emergency of international concern due to evidence suggesting ZIKV infection may be linked to recent clusters of microcephaly in babies born to infected mothers and other reported neurological disorders including Guillain-Barré syndrome (GBS) [2]. According to the WHO, local transmission has been reported in many other countries and territories and will continue to spread to new areas.

There are currently no effective vaccines or therapies against ZIKV. The rapid emergence of ZIKV supports the need for a safe and immunogenic vaccine. This protocol is designed as a Phase 2/2B evaluation of the investigational ZIKV wild-type (wt) DNA vaccine, VRC-ZKADNA090-00-VP. This candidate vaccine is currently being evaluated in a Phase 1 study. This Phase 2/2B study is being advanced rapidly to follow the initiation of the Phase 1 study due to the significant public health need for a vaccine to prevent ZIKV.

1.1. Zika Virus Infection: Etiology, Disease Course and Epidemiology

ZIKV is an arthropod-borne virus (arbovirus) that belongs to the *Flaviviridae* family, genus *Flavivirus*, which also includes dengue (DENV), yellow fever, Saint Louis encephalitis, Japanese encephalitis and West Nile (WNV) viruses. ZIKV is an enveloped virus with a ~10.8 kb, positive sense, single-stranded ribonucleic acid (RNA) genome encoding for structural and non-structural proteins [3, 4].

The name Zika comes from the Zika Forest in Uganda, where the virus was first isolated in 1947 [5]. Genomic sequencing and phylogeny studies have identified three major ZIKV lineages including two African and one Asian [6-8]. Until recently, ZIKV remained endemic to equatorial Africa and parts of Asia. In 2015, an explosive pandemic of ZIKV emerged in South America and spread rapidly throughout the tropical and subtropical Americas, threatening spread to North America [1]. The virus implicated in this current outbreak has been categorized as being of Asian lineage [9].

ZIKV is primarily transmitted to humans by infected mosquitoes, predominantly *Aedes aegypti,* but can be transmitted by other species [6]. ZIKV transmission has also been reported through sexual contact via semen [10], from mother to child during pregnancy or childbirth [11], and through blood transfusion transmission [12].

ZIKV infection causes a fever-like disease with an incubation period (the time from exposure to symptoms) of 3 to 14 days. Most people infected with ZIKV never display symptoms, which

makes it difficult to identify the infection. If the disease presents, it is predominantly mild with symptoms resolving within a week [6, 13, 14]. Symptoms include low-grade fever, myalgia, and maculopapular rash accompanied by conjunctivitis, arthralgia and headache, and less often by edema, sore throat, and vomiting [14]. Information on laboratory changes during ZIKV infection is scarce but laboratory changes may include transient leukopenia, and in some cases thrombocytopenia and liver enzyme elevations [14, 15]. Polyfunctional T-cell activation and cytokine release have also been described during acute ZIKV infection [14]. Though atypical, neurological complications including GBS are being reported in a growing number of cases [16]. Molecular mimicry between glycolipids and surface molecules of infectious agents may explain most of the cases of GBS preceded by infection; etiology of GBS associated with ZIKV infection is currently being investigated [17, 18]. Prenatal ZIKV infection has been associated with adverse pregnancy and birth outcomes, such as microcephaly and other serious neurological anomalies [19-21]; recent evidence shows a causal relationship between ZIKV infection during pregnancy and adverse outcomes in fetuses and infants, including microcephaly [22].

Based on clinical symptoms alone, ZIKV disease cannot be reliably distinguished from infections with DENV, chikungunya (CHIKV) or other viruses that also cause an undifferentiated systemic febrile illness. ZIKV infection diagnosis may be confirmed through serological testing or by viral RNA detection using reverse transcription-polymerase chain reaction (RT-PCR) [23]. Anti-ZIKV immunoglobulin M (IgM) is typically detectible by day 4 through about 12 weeks post onset of symptoms [20, 23]. Serologic cross-reactivity with DENV and other flaviviruses has been reported, especially for subjects with a history of flavivirus infection and therefore background immunity [6, 20, 23].

In February 2016, the US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the ZIKV Mac-ELISA (IgM antibody capture enzyme-linked immunosorbent assay) diagnostic test developed by the Centers for Disease Control and Prevention (CDC) for diagnosis of ZIKV infection by an IgM antibody capture ELISA [20, 24]. In July 2016, the FDA issued an EUA to authorize emergency use of Viracor-IBT Laboratories, Inc.'s ZIKV Real-time RT-PCR Test (Viracor-IBT) for the qualitative detection of RNA from Zika virus in human serum, plasma or urine [24].

Prolonged detection of ZIKV RNA has been observed in whole blood [25]. American Red Cross investigational screening of blood donations demonstrated that ZIKV RNA levels in red blood cells (RBC) may be detected up to 154 days after blood donation with the highest RNA copy levels associated with RBC [26]. ZIKV RNA can be detected by RT-PCR in serum and plasma within 2 to 7 days in the acute stage of infection and in urine for >10 days [27, 28]. However, ZIKV RNA levels in urine have been shown to degrade, making it a less viable option for detection compared to other methods [29]. ZIKV has also been detected in other bodily fluids including semen and saliva [30-32].

1.2. Rationale for Development of VRC-ZKADNA090-00-VP

ZIKV infection may induce long-lasting protective immunity. Survivors of ZIKV infection have detectable humoral and cellular immunity; however, the relative contribution of these to protection is unknown [14, 15].

There is no licensed vaccine or antiviral therapy available for the prevention or treatment of ZIKV infection. The economic losses and added stress on public health infrastructure

experienced in areas of ZIKV transmission along with heightened potential for global spread necessitate vaccine development as a high global priority [33-35].

Investigators at the VRC have developed a plasmid DNA vaccine strategy that has been shown to elicit immune responses against the target pathogen in clinical studies [36, 37]. DNA vaccines have the potential to be manufactured rapidly and are known to induce balanced immune responses that include both humoral and cellular immunity. The potential and experience to date with this vaccine platform warrants continued investigation of DNA vaccines as safe and efficient technology for responding to emerging infectious diseases [37].

The DNA vaccine platform was used in the development of two vaccines for WNV of the *Flavivirus* genus. Similar to the VRC ZIKV DNA vaccines, the WNV investigational vaccines, VRC-WNVDNA017-00-VP and VRC-WNVDNA020-00-VP, express two WNV proteins: prM, a precursor for the M transmembrane protein, and envelope (E) protein of the virus under control of the cytomegalovirus (CMV) promoter and the CMV/R promoter, respectively, and result in the formation of noninfectious subviral particles *in vitro* [38, 39].

In VRC Phase 1 trials, the WNV DNA vaccines were evaluated as safe and well tolerated, and provided compelling evidence that these vaccines can induce neutralizing antibody (NAb) against WNV in healthy adults 18-65 years of age as assessed by a reporter virus particle (RVP) NAb assay and plaque reduction neutralization test (PRNT) [38, 39].

VRC ZIKV DNA vaccines using plasmids VRC 5288 (ZIKV DNA vaccine, VRC-ZKADNA085-00-VP) and VRC 5283 (ZIKVwt DNA vaccine, VRC-ZKADNA090-00-VP) were developed based on prior experience with the WNV DNA vaccine platforms. The two ZIKV vaccines are similar, with the ZIKVwt DNA vaccine expressing the structural prM and E glycoproteins of ZIKV and the ZIKV DNA vaccine expressing prM from ZIKV and a chimeric E protein with part of the sequence of ZIKV and part of sequence of JEV. Expression of prM and E induce the formation of VLPs with antigenic properties comparable to infectious virions [40].

Vaccination with either ZIKV DNA or ZIKVwt DNA elicited ZIKV-specific NAb titers in mice and non-human primates (NHPs). There were no significant differences in NAb titers between animals that received the ZIKV DNA vaccine or animals that received the ZIKVwt DNA vaccine [40]. Based on data reported for WNV DNA vaccines and on animal studies with the VRC ZIKV DNA vaccines, it is expected that the ZIKVwt DNA vaccine will be safe and immunogenic.

1.3. Previous Human Experience with VRC DNA Vaccines

Cumulatively, since the first clinical trial using the VRC DNA vaccine platform in October 2001, more than 3,000 study subjects 6-70 years of age have received one or more injections of VRC DNA vaccines; all evaluated as safe and immunogenic [38, 39, 41-49]. Although a human efficacy study has not yet been completed with any DNA vaccine given alone, clinical trials of WNV DNA vaccines [38, 39], a severe acute respiratory syndrome (SARS) DNA vaccine (VRC-SRSDNA015-00-VP) [43], and an H5 influenza DNA vaccine (VRC-AVIDNA036-00-VP) [41, 50] have provided evidence that DNA vaccines based on the VRC plasmid backbone are safe and can induce NAbs against targeted pathogens. Additionally, a seasonal influenza DNA vaccine (VRC-FLUDNA063-00-VP) has been shown to be safe in 44 children and adolescent subjects ranging in age from 6 to 17 years [unpublished data].

1.4. Human Experience with VRC ZIKV DNA Vaccines

Phase 1 Evaluation: A Phase 1 clinical trial VRC 319 (NCT02840487) began in August 2016 to evaluate the safety and immunogenicity of the ZIKV DNA vaccine and a Phase 1 clinical trial VRC 320 (NCT02996461) began in December 2016 to evaluate the safety and immunogenicity of the ZIKVwt DNA vaccine. At the time of this summary, data quality assurance and monitoring are ongoing, and therefore all reported data are preliminary and should not be considered final. VRC 319 and VRC 320 vaccination schemas and administration routes were selected based on previous experience with the WNV DNA vaccines, the H5 DNA vaccine, and the CHIKV VLP vaccine, all developed by VRC [33, 38, 39, 51].

VRC 319: As of July 24, 2018, 80 subjects have enrolled and received at least one ZIKV DNA vaccination intramuscularly (IM) by needle and syringe. The last study vaccination was administered on February 15, 2017. There have been no serious adverse events (SAEs) related to study product reported in the study. One SAE (appendicitis) was reported as unrelated to study product. Overall, 60 of 80 (75.0%) subjects have had one or more unsolicited adverse events (AEs), with maximum severity being mild (Grade 1) for 36 (45.0%) subjects, moderate (Grade 2) for 18 (22.5%) subjects, severe (Grade 3) for 5 (6.3%) subjects, and life-threatening (Grade 4) for 1 (1.3%) subject. Seventeen (17) mild or moderate unsolicited AEs were assessed as related to study product including: neutropenia (7), lymphopenia (4), leukopenia (2), thrombocytopenia (1); dizziness (1) and paresthesia (1) that occurred in one subject 3 days after vaccination and resolved that same day; and injection site pruritus (1) that occurred on day of vaccination and resolved that day.

Product administrations have been generally well tolerated. Maximum solicited local reactogenicity in the 7 days after product administration was reported as none by 41 of 80 (51.3%) subjects and mild by 39 (48.8%) subjects; no moderate or severe local symptoms have been reported. Mild pain at the injection site was the most common symptom after product administration, reported by 37 (46.3%) subjects; 5 (6.3%) subjects reported mild redness and 1 (1.3%) subject reported mild swelling. With regard to solicited systemic reactogenicity in the 7 days after product administration, 47 of 80 (58.8%) subjects reported none, 29 (36.3%) subjects reported mild, and 4 (5.0%) subjects reported moderate systemic symptoms. No fevers or severe systemic symptoms have been reported. Mild or moderate malaise and headache were the most common symptoms after product administration, reported by 22 (27.5%) and 18 (22.5%) subjects, respectively. Mild or moderate symptoms of myalgia (17, 21.3%), nausea (7, 8.8%), chills (6, 7.5%), and joint pain (4, 5.0%) were reported by subjects less frequently.

VRC 320: As of July 24, 2018, 45 subjects have enrolled and received at least one ZIKVwt DNA vaccination IM by needle and syringe or needle-free injection device, the PharmaJet Stratis® 0.5 mL Needle-Free Jet Injector (PharmaJet). The last vaccination was administered on June 14, 2017. There have been no SAEs related to study product reported in the study. One SAE (ruptured colon) was reported as unrelated to study product. Overall, 32 of 45 (71.1%) subjects have had one or more unsolicited AE with maximum severity being mild (Grade 1) for 17 (37.8%) subjects, moderate (Grade 2) for 12 (26.7%) subjects, severe (Grade 3) for 2 (4.4%) subjects, and life-threatening (Grade 4) for 1 (2.2%) subject. Three (3) AEs were assessed as related to study product including: mild lymphopenia, mild hypertension, and moderate neutropenia, all of which resolved.

With regard to product administrations, maximum solicited local reactogenicity in the 7 days after administration was reported as none by 9 (20.0%) of 45 subjects, mild by 33 (73.3%) subjects, and moderate by 3 (6.7%) subjects; no severe local symptoms have been reported. Mild pain at the injection site was the most common symptom after product administration, reported by 33 (73.3%) of 45 subjects and 3 (6.7%) subjects reported mild swelling. Maximum solicited systemic reactogenicity in the 7 days after product administration was reported as none by 21 (46.7%) of 45 subjects, mild by 20 (44.4%) subjects, and moderate by 4 (8.9%) subjects; no severe systemic symptoms or fevers have been reported. Mild or moderate malaise and headache were the most common symptoms after product administration, reported by 17 (37.8%) and 15 (33.3%) subjects, respectively. Mild or moderate symptoms of myalgia (9, 20.0%), joint pain (8, 17.7%), nausea (2, 4.4%), and chills (2, 4.4%) were reported by subjects less frequently.

Phase 2/2B Evaluation: VRC 705 (NCT03110770) initiated in March 2017 with accrual into Part A; accrual into Part B began in July 2017. Human experience collected in this study is summarized below. At the time of this summary, data quality assurance and monitoring are ongoing, and therefore all reported data are preliminary and should not be considered final.

VRC 705 Part A: As of July 24, 2018, 90 subjects have randomized and received at least one ZIKVwt DNA vaccination IM by PharmaJet. The last vaccination was administered on October 16, 2017. There have been no SAEs related to study product reported in this part of the study. Three (3) SAEs (including: bilateral urolithiasis, bipolar disorder exacerbation, and gunshot wound resulting in death) were reported as unrelated to study product. Overall, 68 of 90 (75.6%) subjects have had one or more unsolicited AE with maximum severity being reported as mild (Grade 1) for 35 (38.9%), moderate (Grade 2) for 28 (31.1%), severe (Grade 3) for 4 (4.4%) subjects, and fatal (Grade 5) for 1 (1.1%) subject.

Regarding product administration, maximum solicited local reactogenicity in the 7 days after administration was reported as none by 9 of 90 (10.0%) subjects, mild by 55 (61.1%) subjects, and moderate by 26 (28.9%) subjects. Mild or moderate pain at the injection site was the most common symptom after product administration, reported by 81 of 90 (90.0%) subjects. Maximum solicited systemic reactogenicity in the 7 days after product administration was reported as none by 38 (42.2%), mild by 40 (44.4%), moderate by 11 (12.2%), and severe by 1 (1.1%) subject. Mild or moderate headache (37, 41.1%), malaise (33, 36.7%, which includes 1 severe event), and myalgia (22, 24.4%) were the most common symptoms reported by subjects after product administration.

VRC 705 Part B: As of July 24, 2018, 1058 subjects have randomized and received at least one product administration with ZIKVwt DNA or PBS by PharmaJet. There have been no SAEs related to study product in this part of the study. Six (6) SAEs (including: seizure, cholelithiasis, ectopic pregnancy, depression, depressive episode, and rhabdomyolysis) were reported as unrelated to study product. Regarding product administration, maximum solicited local reactogenicity in the 7 days after administration was reported as none by 354 of 905 (39.1%) subjects, mild by 411 (45.4%) subjects, moderate by 137 (15.1%) subjects, and severe by 1 (0.1%) subject. Mild or moderate pain at the injection site was the most common symptom after product administration reported by 543 (60.0%) subjects, and as severe by 1 (0.1%) subject. Maximum solicited systemic reactogenicity in the 7 days after product administration was reported as none by 425 (47.0%), mild by 338 (37.3%), moderate by 129 (14.3%), and severe by

11 (1.2%). Mild or moderate headache (312, 34.5%), malaise (275, 30.4%), and myalgia (236, 26.1%) were the most common symptoms reported by subjects after product administration.

1.5. Rationale for Study Product Dose and Administration Method

VRC DNA vaccines have been administered at doses of up to 8 mg, with the majority of injections given at 4 mg. Data from two dose-escalation studies (VRC 004 and VRC 204) indicate that a 4-mg dose offers the combination of a good safety profile, greater ease of administration than an 8-mg dose, and reliable immunogenicity as indicated by laboratory measures of immune response [42, 44]. Preclinical and clinical evaluations to date of plasmid DNA vaccines support the safety and immunogenicity of DNA vaccines at doses up to 8 mg; VRC-ZKADNA090-00-VP will be evaluated at doses of 4 mg/mL and 8 mg/mL in **Part A**. Preliminary data from VRC 319, VRC 320 and VRC 705 Part A indicate that a 4 mg dose administered IM by PharmaJet at weeks 0, 4 and 8, offers the combination of a good safety profile, ease of administrations and reliable immunogenicity and as a result, this regimen was selected for **Part B.**

In previous studies, DNA vaccines have been administered by IM, subcutaneous (SC), or intradermal routes using either standard needle and syringe or needle-free injection device. The use of a needle-free injection system was found to be superior to needle and syringe by offering a significant contribution to the elicited immunogenicity [52].

In March 2016, Biojector (Biojector 2000® needle-free injection system, Bioject Medical Technologies, Tigard, OR), which was used in previous VRC DNA vaccine studies, became unavailable. Therefore, investigational products in this study will be administered using the PharmaJet, a similar needle-free injection device.

PharmaJet is intended to deliver various medications and vaccines to adults and children either IM or SC by means of a narrow, high velocity fluid jet. PharmaJet is a Class II medical device that holds a General Use 510(k) marketing clearance from the FDA and received the *Performance, Quality and Safety* (PQS) pre-qualified certification from the WHO (#E008/050). Energy to propel the fluid ("liquid needle") is supplied by a hand-held, spring-powered injector. Immunogenicity studies have been conducted in rhesus macaques in which animals received doses of the ZIKVwt DNA vaccine via PharmaJet showed an increase in NAb production following immunization in both groups [40].

In this study, 'product administration' describes the completion of all PharmaJet injections (either 2 or 4) needed to give the full dose assigned at a visit.

In **Part A**, each subject will receive the ZIKVwt DNA vaccine administered by PharmaJet on Day 0, Week 4 and Week 8. Group 1 will receive a total dose of 4 mg split into two 0.5 mL needle-free injections, with one IM injection given into each arm. Group 2 will receive a total dose of 4 mg split into four 0.5 mL needle-free injections (using diluent to reach the full 0.5 mL volume), with one injection given IM into each arm and each leg. Group 3 will receive a total dose of 8 mg split into four 0.5 mL needle-free injections, with one injection given IM into each arm and each leg. These regimens will help us determine if the optimal regimen is to administer the full dose into one limb or to split the dose among limbs.

In **Part B,** each subject will receive the ZIKVwt DNA vaccine or placebo administered by PharmaJet on Day 0, Week 4 and Week 8. Group 4 will receive a total dose of 4 mg split into

two 0.5 mL needle-free injections, with one IM injection given into each arm and Group 5 will receive two 0.5 mL needle-free injections of placebo, with one IM injection given into each arm.

1.6. Rationale for the Study Population

In **Part A**, healthy adults 18 years of age (or the site-specific minimum age that applies to adults) to 35 years of age have been chosen as the target population.

In **Part B**, the population will expand to include healthy adolescents 15-17 years of age. Therefore, healthy subjects 15-35 years of age have been chosen as the target population for **Part B**. According to the WHO, more than 15 million of the 135 million (11%) live births worldwide are among girls aged 15-19 years [53]. Therefore, this study targets age groups of the highest reproductive potential who will likely be the initial recipients of a successful ZIKV vaccine.

The maximum age for the study target population is 35 years of age. This is based on data suggesting an increased risk of GBS with increasing age, so the study population excludes those who might be at higher risk for GBS [54-56].

1.7. Assessment of Immunogenicity

In this study, specimens to evaluate immunogenicity will be collected at baseline and at specified time points. The primary immunogenicity time point is 4 weeks after receipt of the last product administration. ZIKV-specific humoral immune responses will be assessed at clinical visits through 32 weeks after receipt of the first product administration in **Part A** and 96 weeks after receipt of the first product administration in **Part B**. ZIKV-specific cellular immune responses at baseline and select timepoints after product administration may also be assessed in Part A subjects and at designated sites in Part B.

NAbs are a well-established correlate of protection against flavivirus infection. A pseudo-infectious ZIKV RVP NAb assay will be performed at baseline and 4 weeks after the last product administration for a secondary endpoint as previously described for WNV [38, 39] and possibly on stored samples from other study time points as an exploratory endpoint. Use of the RVP approach to detect and enumerate NAbs offers several advantages as compared to the traditional PRNT including: increased precision, speed, and ability to perform assays under biosafety level-2 conditions in large scale (allowing analysis in replicate using a large number of dilutions). The normalization criteria used to validate assay results are derived directly from the "percentage law" (law of mass action) and confer a significant improvement in assay-to-assay reproducibility and accuracy. Extensive analysis of the neutralization potency of several well characterized monoclonal antibodies [57, 58] reveal agreement with published values obtained using the PRNT and BHK-21 cells [59].

Briefly, ZIKV RVPs for use in neutralization assays will be produced in HEK-293T cells by co-transfection with plasmids encoding a green fluorescent protein (GFP)-expressing WNV replicon and the structural proteins of the ZIKV H/PF2013 strain [60]. ZIKV RVPs will be incubated with serial three-fold dilutions of heat-inactivated sera and added to Raji cells expressing the attachment factor DC-SIGNR. Infected cells expressing GFP will be measured two days post-transfection using flow cytometry or other assay readout. The dilution of sera required to neutralize half the infection events (EC50) will be estimated by non-linear regression using Graph Pad Prism. ZIKV NAbs elicited by immunization with VRC-ZKADNA090-00-VP have been recently described [51].

Exploratory assays may include T-cell analyses by Intracellular Cytokine Staining (ICS) and/or ELISpot assay as previously described for WNV [38, 39]. Other exploratory immunogenicity assays may be performed with stored samples.

To evaluate cross-reactivity of ZIKV-specific responses with responses to other flaviviruses, pre-existing responses to DENV, yellow fever, Japanese encephalitis, and WNV at baseline may be evaluated retrospectively, along with cross-reactivity at 4 weeks after last product administration.

The immunogenicity testing will be performed at the NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL, Gaithersburg, MD, US) following Good Clinical Laboratory Practice (GCLP) regulations and may also be performed in research laboratories at the VRC, the Laboratory of Viral Diseases, Viral Pathogenesis Section, NIAID, NIH, Z-Quick, University of Miami Life Science and Technology Park (Miami, FL, US), or by other approved collaborators. New assays to characterize and quantify Zika antibodies are currently being developed and new collaborators and/or testing laboratories may be used in the future.

1.8. ZIKV Infection Assessment

Subjects who develop any possible sign or symptom of ZIKV infection at any time following the first product administration will be clinically evaluated by the trial site as soon as possible. In **Part A**, subjects can be diagnosed at the designated primary diagnostic laboratory (PDL), the University of Washington (Seattle, WA, US), by PCR evaluation of blood and/or urine samples or by site standard procedures.

Part B of the study is designed to evaluate the efficacy of the selected vaccine regimen compared to placebo. In order to evaluate vaccine efficacy, all possible cases of ZIKV infection are required to be diagnosed by the PDL by PCR evaluation of blood and urine samples, except in the case of suspected hemorrhagic fever, in which blood and urine samples must be sent to the CDC's Diagnostic and Reference Laboratory, Arbovirus Diseases Branch (Fort Collins, CO, US). Additionally, sites may follow a local standard of care to diagnose suspected ZIKV infection by PCR testing. Research specimens may also be collected for viral evaluation at the request of the Investigational New Drug (IND) Sponsor.

In **Part B,** regardless of symptoms, blood will also be collected for research on a routine basis per the Schedule of Evaluations tables in Appendix III. These stored samples will be retrospectively evaluated for ZIKV by PCR by Battelle, Biomedical Research Center (West Jefferson, Ohio, US). This assessment is not intended to replace real-time evaluation of possible symptomatic ZIKV infections and will not provide a diagnosis nor will it guide clinical care. However, this assessment will be performed to aid in the evaluation of exposure to ZIKV or possible asymptomatic ZIKV infections throughout the trial.

2. STUDY PRODUCTS

Study products are manufactured under current Good Manufacturing Practice (cGMP) regulations.

2.1. VRC-ZKADNA090-00-VP, ZIKVwt DNA Vaccine

VRC-ZKADNA090-00-VP was manufactured by the VRC Pilot Plant operated under contract by Leidos Biomedical Research, Inc. (Frederick, MD, US). The VRC-ZKADNA090-00-VP drug substance consists of a single closed-circular plasmid DNA (VRC 5283) that encodes the precursor transmembrane M (prM) and envelope (E) proteins from the H/PF/2013 strain of ZIKV (GenBank number AHZ13508.1) derived from a French Polynesian isolate and identical or highly related to strains circulating in the Americas.

The plasmid CMV/R promoter consists of translational enhancer region of the CMV immediate early region 1 enhancer (CMV-IE) substituted with the 5′-untranslated human T cell leukemia virus type 1 (HTLV-1) R-U5 region of the human T cell leukemia virus type 1 HTLV-1 long terminal repeat (LTR), and has been shown to optimize gene expression further [61]. This promoter has been evaluated in preclinical safety studies as well as several clinical trials of DNA vaccines for HIV (BB-IND 11750), WNV (BB-IND 12933), Ebola (BB-IND 11294), SARS (BB-IND 11995) and avian influenza (BB-IND 13197).

The drug product is formulated in phosphate buffered saline (PBS). Vials are aseptically filled to a volume of 1.2 or 1.5 mL with 4 mg/mL of plasmid. More details related to vaccine preparation, manufacturing, and preclinical studies can be found in the Investigator's Brochure (IB).

2.2. VRC-PBSPLA043-00-VP, Placebo and Diluent

VRC-PBSPLA043-00-VP, sterile PBS, is the placebo and diluent for the ZIKVwt DNA vaccine.

2.3. Preclinical Safety and Immunogenicity Studies of VRC-ZKADNA090-00-VP

Non-clinical, non-GLP immunogenicity studies in mice and NHPs were conducted at the VRC with the ZIKVwt DNA vaccine administered IM. Results confirmed that the vaccine is immunogenic, protects against ZIKV challenge, and induces neutralizing antibodies [40].

GLP toxicology studies are not planned for VRC-ZKADNA090-00-VP because the vector backbone has been extensively tested with other VRC DNA vaccines and similar inserts (WNV) were previously tested [38, 39, 62, 63].

More details on the preclinical studies with VRC-ZKADNA090-00-VP can be found in the IB.

3. STUDY OBJECTIVES

3.1. Primary Objectives

Part A:

- To evaluate the safety and tolerability of VRC-ZKADNA090-00-VP in healthy adults when administered IM at a dose of 4 mg IM by needle-free injection device.
- To evaluate the safety and tolerability of VRC-ZKADNA090-00-VP in healthy adults when administered IM at a dose of 8 mg IM by needle-free injection device.

Part B:

- To evaluate the safety and tolerability of VRC-ZKADNA090-00-VP in healthy adults and adolescents when administered IM at a dose of 4 mg by needle-free injection device compared to placebo.
- To evaluate the efficacy of VRC-ZKADNA090-00-VP by comparing incidence rates of virologic ZIKV cases in vaccine and placebo recipients.

3.2. Secondary Objectives

Part A:

- To evaluate the magnitude and the frequency of ZIKV-specific antibody response as measured by neutralization assay at 4 weeks after the last product administration.

Part B:

- To evaluate the magnitude and the frequency of ZIKV-specific antibody response as measured by neutralization assay at 4 weeks after the last product administration.
- To compare incidence rates of subclinical cases of ZIKV infection in vaccine and placebo recipients.

3.3. Exploratory Objectives

Part A:

- To characterize ZIKV-specific antibody and T cell responses at specified time points.
- To evaluate the durability of ZIKV-specific immune responses.
- To evaluate the immunogenicity of split dose injections administered to 2 or 4 limbs.

Part B:

- To evaluate the magnitude and duration of ZIKV viruria or viremia.
- To characterize ZIKV-specific antibody and T cell responses at specified time points throughout the study.
- To evaluate the durability of ZIKV-specific immune responses.
- To compare the incidence of DENV disease in the vaccine and placebo recipients.
- To compare incidence rates of symptomatic cases of ZIKV infection in vaccine and placebo recipients.

4. STUDY DESIGN AND CLINICAL PROCEDURES

This is a Phase 2/2B multicenter, randomized study of the ZIKVwt DNA vaccine in healthy adults and adolescents. The hypotheses are that the vaccine regimen is safe and induces a neutralizing antibody response to ZIKV. **Part A** will target healthy adults only. **Part B** includes adolescents in the study population. Therefore, **Part B** study sites will have the option to enroll adolescents and adults, or sites may choose to enroll only an adult population.

This study will be conducted at trial sites that are located in areas of confirmed or projected active transmission of ZIKV infection. The allotted randomization slots per site for **Part A** will be defined per site capability to enroll rapidly. The allotted randomization slots per site for **Part B** will be assigned based on site capacity and local epidemiological data, the number of site slots may be increased or decreased as the epidemic shifts. All sites participating in **Part B** will be asked to monitor their local epidemiologic data as reported by regional or other authorities and be prepared to report this data to the IND Sponsor, when applicable and requested. Each subject will be on study for about 32 weeks in **Part A** and 96 weeks in **Part B**. The study schema is in Table 1.

Table 1: Study Schema

Part A							
Group	**Subjects**	**Total Dose**	**Number of Injections per Dose**	**Number of Limbs: Location of Injections**	**Administration Schema**		
					Day 0	**Week 4**	**Week 8**
1	30	4 mg	2	2 limbs: both arms	DNA	DNA	DNA
2	30	4 mg	4	4 limbs: both arms and legs	DNA	DNA	DNA
3	30	8 mg	4	4 limbs: both arms and legs	DNA	DNA	DNA
Total	**90***	Study product is administered IM by needle-free injection device.					
*Accrual up to a total of 100 subjects is permitted if additional subjects are needed for safety evaluations.							
Part B							
Group	**Subjects**	**Total Dose**	**Number of Injections per Dose**	**Number of Limbs: Location of Injections†**	**Administration Schema**		
					Day 0	**Week 4**	**Week 8**
4	1200	4 mg	2	2 arms	DNA	DNA	DNA
5	1200	0	2	2 arms	Placebo	Placebo	Placebo
Total	**2400**	Study product is administered IM by needle-free injection device.					
† Preferred location of injections is in both arms. Administration in the thighs may be allowed with IND Sponsor approval.							

4.1. Eligibility Criteria

The study is designed for the participation of healthy adults and adolescents. All inclusion and exclusion criteria must be met for eligibility.

4.1.1. Inclusion Criteria

A subject must meet all of the following criteria:

1. **Part A**: 18 to 35 years of age;

   Part B: 15 to 35 years of age
2. **Part A**: Available for clinical follow-up through Study Week 32;

   Part B: Available for clinical follow-up through Study Week 96
3. Able to provide proof of identity to the satisfaction of the clinician completing the enrollment process
4. Able and willing to complete the informed consent/assent process
5. Able and willing to complete the Assessment of Understanding and to verbalize understanding of all questions answered incorrectly prior to signing consent/assent
6. Willing to donate blood and urine to be stored and used for future research
7. In good general health without clinically significant medical history
8. Physical examination and laboratory results without clinically significant findings within the 56 days prior to randomization
9. Weight > 30 kg
10. Agree not to receive any licensed or investigational flavivirus vaccines through 4 weeks after the last product administration
11. **Part A**: Accessible injection sites on each limb as follows: 1 injection site in the deltoid muscle of each arm and 1 injection site in the vastus lateralis muscle of each anterolateral thigh.

    Part B: Accessible injection sites on the deltoid muscle of each arm. Injection sites on the vastus lateralis muscle of the anterolateral thighs may be allowed with IND Sponsor approval if an injection site on each deltoid muscle is not available.

*Laboratory criteria within **56 days prior to randomization**:*

12. Hemoglobin within site institutional normal limits
13. Absolute neutrophil count (ANC) within site institutional normal limits
14. Total lymphocyte count ≥ 800 cells/mm^3
15. Platelets = 125,000 – 510,000 cells/mm^3
16. Alanine aminotransferase (ALT) ≤ 1.5 x upper limit of normal (ULN) based on site institutional normal range for respective age group

17. Serum creatinine ≤ 1.2 x ULN based on site institutional normal range for respective age group
18. Negative result on an HIV test that meets local standards for identification of HIV infection

Criteria applicable to women and adolescents of childbearing potential:

19. Negative result on a human chorionic gonadotropin pregnancy test (urine or serum) on day of randomization before receiving study product
20. Agree to use effective means of birth control from at least 21 days before randomization through 12 weeks after the last product administration

Criteria applicable to adolescents:

21. Capability of the parent/guardian of the minor to understand and comply with planned study procedures.
22. Capability of the minor and their parent/guardian to provide assent/informed consent

4.1.2. Exclusion Criteria

A subject will be excluded if one or more of the following conditions apply:

Criteria applicable to women and adolescents of childbearing potential:

1. Breast-feeding or planning to become pregnant while participating through 12 weeks after the last product administration

Subject has received any of the following:

2. More than 10 days of systemic immunosuppressive medications or cytotoxic medications within the 4 weeks prior to randomization
3. Any systemic immunosuppressive medications or cytotoxic medications within the 14 days prior to randomization
4. Blood products within 16 weeks prior to randomization
5. Immunoglobulin within 8 weeks prior to randomization
6. Investigational research agents within 4 weeks prior to randomization or planning to receive investigational products while on the study
7. Any vaccination within 2 weeks prior to randomization
8. Any live attenuated vaccination within 4 weeks prior to randomization
9. Current anti-TB prophylaxis or therapy

Subject has any of the following:

10. Confirmed history of ZIKV infection (as reported by subject)
11. Serious reactions to vaccines
12. Chronic angioedema or chronic urticaria
13. Asthma that is not well-controlled

14. Diabetes mellitus (type I or II)
15. Clinically significant autoimmune disease or immunodeficiency
16. Hypertension that is not well controlled
17. Bleeding disorder diagnosed by a doctor (e.g. factor deficiency, coagulopathy, or platelet disorder requiring special precautions)
18. Significant bruising or bleeding difficulties with IM injections or blood draws
19. Malignancy that is active or history of a malignancy that is likely to recur during the period of the study
20. Seizure or treatment for a seizure disorder within the last 3 years
21. Asplenia, functional asplenia or any condition resulting in the absence or removal of the spleen
22. History of Guillain-Barré Syndrome
23. Psychiatric condition that may preclude compliance with the protocol; past or present psychoses; or a history of suicide plan or attempt within 5 years prior to randomization
24. Any medical, psychiatric, or social condition that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a subject's ability to give informed consent.

4.2. Clinical Procedures and Evaluations

Evaluation of this investigational vaccine will include laboratory tests, medical history, physical examination by clinicians and subject self-assessment. The schedule of study visits is shown in the Schedule of Evaluations tables in Appendix III. As per NIH Clinical Center guidelines, total blood volume drawn from adult subjects (who weigh at least 50 kg) will not exceed 550 mL in any 8-week period; total blood volume from each adolescent subject will not exceed 9.5 mL/kg in any 8-week period. Sites must also follow institutional policy for blood collection from adults and adolescents as applicable.

4.2.1. Pre-screening

Subjects will be recruited through Institutional Review Board (IRB)/ Ethics Committee (EC) - approved advertising.

To identify potential study subjects, study staff may discuss the VRC 705 clinical trial with those who express interest. Study staff may use an interview questionnaire to obtain self-reported medical history in order to determine if the subject may be eligible based on protocol inclusion and exclusion criteria. Potential study subjects who appear to be eligible may continue to screen for this study. No study-specific interventions may be done during pre-screening.

4.2.2. Screening and Enrollment

The screening process may occur over one visit or multiple visits in order for the site to fully assess each subject's eligibility to participate in this study. Table A: Schedule of Evaluations – Screening is available in Appendix III. Screening procedures must be completed within the 56-day screening window. The informed consent form (ICF)/ assent form may be signed more than

56 days before study randomization and does not need to be re-signed if outside of this window, unless required by local regulations or an updated form becomes available.

Assessment of Understanding: The Assessment of Understanding (AoU) is a tool to help study staff confirm the subject's understanding of the consent/assent information. The AoU **must** be completed before the subject signs the consent/assent form. For adolescent subjects, the AoU will be completed with the parent/guardian present. Incorrect answers on the AoU must be reviewed with the subject.

Informed Consent: In clinical research, informed consent is a process in which a competent individual is fully informed about the nature, benefits and risks of a clinical trial and makes an informed decision on his/her study participation. Informed consent will be presented and discussed in a language and at a level that is understandable to the potential subject (and parent/ guardian, if applicable).

Appropriately trained and delegated study staff must review the ICF with each potential subject (and parent/guardian, if applicable). Before screening procedures can be performed, informed consent must be obtained, and the form must be signed by the subject.

Template main and parental ICFs are provided in Appendix I. Per Section 8.4, sites must use the templates to develop site-specific forms as needed, adding relevant information as required by site institutional/local/national regulations.

Assent of Adolescents: Adolescents are expected to be able to provide informed consent. However, if the adolescent's age is below the legal age of consent per country regulations, the parent/guardian must also provide consent and sign the ICF (or both parents if required by site regulatory authorities) or the site may use an assent form.

A template assent form is provided in Appendix I. Per Section 8.4, sites must use the template to develop site-specific forms as needed, adding relevant information as required by site institutional/local/national regulations.

Enrollment: All subjects who sign the consent or assent forms **must** be enrolled in the database following completion of the informed consent/assent process.

During Screening:

- **Medical History and Physical Examination**: The PI or designee must obtain a medical history and perform a physical examination including collection of vital signs, height and weight within 56 days before randomization.
- **Injection Site Assessment**: Clinical staff should assess potential injection sites in the deltoid muscle of each arm and in the vastus lateralis muscle of each anterolateral thigh, as applicable. Clinical staff should avoid administering an injection in an area that has an injury, local skin problem or significant tattoo that interferes with evaluation of the injection site after product administration.
- **Pregnancy Prevention Counseling and Pregnancy Testing**: Clinical staff must perform pregnancy prevention counseling on female subjects of childbearing potential to evaluate if subjects are able to meet the birth control eligibility criteria. Pregnancy test results must also be confirmed as negative for these subjects during screening.

- **HIV Prevention Counseling**: During screening, HIV counseling must be performed on all subjects being tested for HIV to ensure the subject is aware of how to reduce risk of and avoid HIV infection. Every attempt must be made to provide the HIV test results to the subjects.
- **Blood Sample Collection**:
  - Samples for clinical evaluation of eligibility criteria must be completed no more than 56 days before randomization. Tests may be repeated as needed based on clinical judgment to confirm eligibility or if there is a suspected change in health status.
  - Samples for research must be collected during screening. However, research samples obtained more than 56 days before randomization do not need to be repeated. Some samples collected during screening may be used for assay validation and site proficiency testing.
- **Eligibility Review**: Based on results from the physical examination, medical history evaluation, blood tests and any additional health assessments performed during screening, the PI or designee will determine if subjects qualify to participate in this study and confirm by documenting on the applicable data collection forms and in the database. For subjects who are not eligible, the reason(s) must be recorded.

4.2.3. Randomization

Visit 02 (Day 0) is defined as the day of study randomization and first product administration. Table B: Schedule of Evaluations – **Part A** and Table C: Schedule of Evaluations – **Part B** are available in Appendix III.

Before Randomization:

- **Pregnancy Prevention Counseling and Pregnancy Testing**: Pregnancy prevention counseling must be conducted, and pregnancy test results must be confirmed negative for females of childbearing potential.
- **Medical History Review and Targeted Physical Examination**: Review health status and current medications including recent vaccinations, measure vital signs, re-assess potential injection sites, and verify all eligibility criteria.

  If a subject presents with fever or other signs of illness during the first product administration visit, do not randomize the subject and do not order or administer study product. Instead, review the subject's medical history and conduct a targeted physical examination, as needed. If there are no exclusionary findings or significant illness and the subject becomes well, the randomization visit may be rescheduled within the 56-day allowable screening period. If Visit 02 cannot be rescheduled within the 56-day window, re-test and re-evaluate all required screening parameters in order to ensure eligibility prior to rescheduling the subject for randomization.
- **Eligibility Confirmation**: Eligibility criteria must be reviewed prior to randomization in the study database.

Randomization: Subjects are electronically randomized in the database based on a randomization plan prepared in advance by the Protocol Statistician. Randomization and product administration must both occur on the same day at Visit 02 (Day 0).

Baseline Values for Future Health Assessments: Visit 02 evaluations and medical history that were obtained prior to the first product administration will be used as the baseline for all future safety assessments. If a blood test was not performed at Visit 02 or if results were not obtained due to an error, the values that were obtained during screening evaluations may be used as the baseline for all future safety assessments.

4.2.4. Product Administration

Before Ordering Study Product: Pregnancy prevention counseling must be conducted, and pregnancy test results must be confirmed negative for females of childbearing potential. Subjects must be clinically evaluated with a medical history review and injection site assessment. Blood samples must be collected after randomization but prior to product administration per Tables B and C in Appendix III for **Part A** and **Part B**, respectively.

For the Second and Third Product Administrations: If a subject presents with fever or other signs of significant illness on the day of the product administration visit, do not order or administer study product. Unscheduled visits may be used to evaluate the subject's condition and the administration visit should be rescheduled within the allowable visit window.

If a subject is undergoing evaluation and/or treatment for a medical condition at the time of the second or third scheduled administration visit, then the visit should be delayed and discussed with the IND Sponsor.

To schedule a product administration visit outside of the allowable visit window, the site must obtain IND Sponsor approval.

Ordering Study Products: Sites must follow their standard operating procedures to order study products from the Pharmacy.

4.2.4.1. Product Administration Procedures

All subjects in **Part A** will receive the ZIKVwt DNA vaccine. Therefore, **Part A** of the study is open-label and blinding of treatment assignment is not required.

In **Part B**, subjects will receive either the ZIKVwt DNA vaccine or placebo. Therefore, all injections will be administered in a blinded manner according to the randomization assignment. Neither the study staff nor the subjects will know if the injections are vaccine or placebo.

Administer injections to the subject as soon as possible after the syringes are filled. All 2 or 4 PharmaJet injections per dose should be administered consecutively, one given immediately after the other and so forth. The maximum allowable time between all 2 or 4 injections is 1 hour (60 minutes). If all injections per dose are not given within 1 hour, administration of any remaining injections must be approved by the IND Sponsor before proceeding.

Both the staff administering study product and the subject receiving study product must wear safety glasses during product administration. The PharmaJet apparatus should be pressed firmly against the subject's skin, in the area over the lateral deltoid muscle of the arm or the vastus lateralis muscle of the anterolateral thigh. This technique compresses the SC space, bringing the

skin and muscle into close proximity, to deliver the vaccine or placebo to the muscle. Even in obese subjects, these areas have comparatively little SC fat accumulation; thus, they are reliable sites to achieve IM fluid penetration. Refer to the IB for more information and instructions for use of the PharmaJet device.

Study staff must practice universal precautions and dispose of the syringes and the needle-free device disposable components in accordance with the site policy and practices.

4.2.5. Diary Card and Follow-Up after Product Administration

Immediately after Product Administration: After each completed product administration (the required sets of 2 or 4 injections are given), subjects must be observed for at least 15 minutes. After 15 minutes, vital signs including temperature, blood pressure, and pulse must be measured and recorded. The injection sites must be inspected for evidence of local reaction and the subject must be assessed for any signs or symptoms of an immediate reaction before leaving the clinic. Acute medical care will be provided to subjects for any significant adverse reactions to study product.

Diary Card: Subjects will be given a Diary Card to use as a memory aid, on which to record the solicited signs and symptoms daily for 7 days after each product administration. The site may use the paper diary card as a source document, or clinical staff notes obtained by telephone or in-person interview may be used as the source for the information that is recorded in the database.

The solicited signs and symptoms on the diary card will include the following parameters: unusually tired/feeling unwell, muscles aches (other than at injection sites), headache, chills, nausea, joint pain, and pain/tenderness at the injection sites. Subjects will also record the highest measured temperature per day and measurement per day of the largest diameter for redness and swelling at the injection sites, if applicable. Subjects should be instructed to record the greatest symptom or measurement overall when evaluating multiple injection sites. Subjects will be provided with devices to measure temperature and diameter.

Follow-Up after Product Administration: Subjects are informed to contact the clinic or seek immediate medical attention, if necessary, at any time during the study if they experience any concerning signs or symptoms. Follow-up on subject well-being will be performed by telephone or in-person between 7 to 10 days after each product administration. At this time, clinical staff will also review the solicited diary card information.

Events that should prompt clinical evaluation include rash, urticaria, skin changes at the injection site, fever of 38˚C (Grade 1) or higher, or any concerning systemic symptom. Subjects should be counseled to report these symptoms as soon as they occur. These symptoms could indicate an injection site reaction or potential ZIKV infection and therefore must carefully be evaluated by the PI or designee.

4.2.6. Follow-Up Visits and Scheduling

Study follow-up will continue via clinical visits after the first product administration through 32 weeks in **Part A** and 96 weeks in **Part B**. Clinical visits may include a health status review, vital signs and/or blood collection. The scheduled visits are based on intervals of time after each product administration visit. If study product is not given as scheduled, then the follow-up visits should be scheduled based on the date that the last study product was given. When product is not given, the corresponding follow-up phone contact (A visit) may be omitted.

The schedule of visits, allowable windows (range of consecutive days) for completing the visits, terms of rescheduling visits, and evaluations performed at each visit are shown in the tables in Appendix III. After Visit 02, deviations from the visit windows are discouraged and will be recorded as protocol deviations but are permitted, at the discretion of the IND Sponsor.

As of protocol version 5.0 approval, study visits 15, 17, 19, 21, 23, and 25 will not be performed. The applicable study visits have been removed from the Schedule of Evaluations table for Part B (Appendix III).

4.2.6.1. Important Information about Shifting Study Visits

Study visits are scheduled a specific number of days apart in order to obtain blood samples for safety and research data at critical time points after each product administration. Note that these days are calendar days and not working business days. Therefore, the "Day of Study" is important to consider when scheduling or rescheduling a subject visit. All study visits are scheduled based on the date of the most recent product administration. Below is further explanation on scheduling.

Visit 02 (Day 0) = first product administration visit. Study Visits 02A and 03 must be scheduled based on the date of the first product administration.

Visit 03 = second product administration visit. Study Visits 03A through 04 must be scheduled based on the date of Visit 03. For example, if Visit 03 occurs +15 calendar days outside of the visit window, then Visits 03A and 04 must also be moved ahead +15 calendar days. If the second product administration does not occur, then schedule all follow-up visits based on the date of the first product administration.

Visit 04 = third product administration visit. Study Visits 04A through 26 must be scheduled based on the date of Visit 04. For example, if Visit 04 occurs +20 calendar days outside of the visit window, then visits 04A through 26 must also shift (or be moved forward) +20 calendar days. If the third product administration does not occur, then schedule all follow-up visits based on the date of the second product administration.

4.2.7. Pregnancy during the Study

Female subjects of childbearing potential will receive pregnancy prevention counseling throughout the study. Women will be asked to notify the site immediately if they suspect or learn they are pregnant during this study. In case of pregnancy, subjects will be removed from the product administration schedule but may have limited clinic contacts and blood draws at the discretion of the site PI and IND Sponsor.

Each site will have a prepared list of resources for any woman who becomes pregnant during the study. Sites will also refer pregnant women to the CDC guidance on how to protect themselves from getting ZIKV infection (https://www.cdc.gov/zika/pregnancy/protect-yourself.html).

All pregnancies that begin during the study will be recorded. The site must contact the subject to learn the outcome of a pregnancy that begins during the study.

4.3. Evaluation of ZIKV Infection During the Study

4.3.1. ZIKV Infection Definition

A virologic case of ZIKV infection will be defined as a virologically confirmed ZIKV infection irrespective of symptoms.

A subclinical case of ZIKV infection will be defined as a virologically confirmed ZIKV infection without clinical signs or symptoms of ZIKV. Subclinical cases of ZIKV infection will be identified by retrospective PCR testing of stored whole blood samples.

A symptomatic case of ZIKV infection will be defined as a virologically confirmed ZIKV infection in conjunction with at least one clinical sign and/or symptom. According to the CDC, the most common symptoms of ZIKV are fever, rash, joint pain, or conjunctivitis (red eyes). Other common symptoms include muscle pain and headache.

4.3.2. Unscheduled Collection of Samples for Suspected ZIKV Infection

At any time during the study, if a subject exhibits any sign or symptom possibly consistent with a ZIKV infection, PI or designee must attempt to diagnose the infection rapidly. PCR testing must be used to test for ZIKV infection because vaccine-induced antibodies could be detected by antibody-based diagnostic tests and even mimic the antibody profile of acute or remote ZIKV infection.

Sample collection for diagnostic testing may occur during a scheduled study visit or an unscheduled visit may be conducted. All samples sent to the PDL will be tested using the RealStar® Zika Virus RT-PCR to test for ZIKV specific RNA. Upon site request, the PDL will also run the TrioPlex Real-time RT-PCR for the differentiation of ZIKV, DENV and CHIKV RNA. The site should request TrioPlex when there is suspicion of DENV and/or CHIKV based on clinical symptoms or local epidemiology in order to differentiate from ZIKV infection.

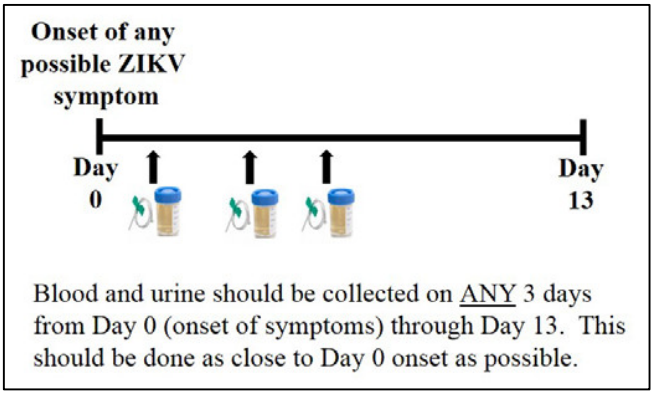
Because diagnostic testing based on ZIKV-specific antibody tests could lead to inadvertent unblinding, study staff will remind subjects that it is preferable that no testing for ZIKV infection be done outside of the trial during study participation unless required to provide care to the subject, such as if needed while traveling. If this occurs, virologic (PCR-only) test results should be provided to the study team as available so that proper documentation of ZIKV infection can occur. In addition to laboratory testing, subjects should always be evaluated using clinical judgment, local requirements, and the current CDC or WHO definitions of ZIKV infection: https://wwwn.cdc.gov/nndss/conditions/zika-virus-disease-and-zika-virus-congenital-infection/case-definition/2016/ or http://www.who.int/csr/disease/zika/case-definition/en/ respectively.

In **Part A**, diagnostic testing of suspected ZIKV infections by virus detection (e.g., PCR) may be done through the PDL or by the site's local standard testing procedures. It is recommended that serum and urine be collected for laboratory testing but there is no requirement for the type or number of samples that should be collected and tested. Note that only samples collected on one day are recorded in the database if collected, additional samples must be recorded and tracked in the subject study file.

In **Part B**, diagnostic testing of suspected ZIKV infections by virus detection (e.g., PCR) must be done through the PDL. When possible, sites may also use local standard testing procedures

using PCR only to diagnose suspected ZIKV infections. As shown in Figure 1, up to 3 blood samples for serum (8 mL each) and up to 3 samples of urine (minimum of 10 mL) should be collected as soon as possible after the onset of a sign or symptom, preferably within 3 days of the onset of the sign or symptom. Study clinicians should attempt to collect blood and urine on 3 different dates within the first 13 days after illness onset. The collection dates do not need to be consecutive. Any samples collected within the first 13 days of illness should be sent for testing, even if all 3 samples of biological type were not collected. Sites may collect additional blood and other bodily fluids if instructed by the IND Sponsor.

Figure 1: Evaluation for Symptomatic ZIKV Infection in Part B



Test Results: Subjects will be informed of all diagnostic test results from the PDL as soon as the results are available. Any one positive PCR result, even in the event of discrepant results between the PDL and local laboratory, should be treated as a positive for the purposes of clinical care and reporting requirements. Repeat testing may need to be performed to confirm or follow the course of an infection.

4.3.2.1. Suspected Hemorrhagic Fever

If at any time a subject exhibits possible signs of hemorrhagic fever (HF), including hypotension and purpura, the subject should be evaluated as soon as possible. Once symptoms of HF are known, diagnostic testing of samples must first occur through testing at the CDC, and samples must not be sent to the PDL until instructed by the IND Sponsor or Sponsor's contract research organization (CRO) to do so. Collection procedures for subjects with suspected HF are the same as they are for suspected ZIKV infections as follows: **Part A**: collect blood and urine as soon as possible; **Part B**: collect 3 blood samples for serum (8 mL each) and 3 samples of urine (minimum of 10 mL) as soon as possible after the onset of a sign or symptom within the first 13 days.

Backup samples should be retained by the site until the evaluation for HF is complete. Only if reported as negative for HF and notified by the IND Sponsor or sponsor representatives to proceed may backup samples be sent to the PDL for further testing.

4.3.3. Scheduled Collection of Research Samples for Asymptomatic ZIKV Infection (Part B only)

The purpose of routine research sample collections is to retrospectively identify possible cases of ZIKV infection in the viremic phase, since many ZIKV infections are often subclinical with mild to no symptoms. Subjects will not receive the results of these evaluations.

- Blood Collection: All sites will collect blood samples for research, obtained at scheduled follow up visits as noted in Appendix III, Table C: Schedule of Evaluations – Part B.
- Urine Collection: As of protocol version 5.0, collection of urine samples for research is discontinued.

4.3.4. ZIKV Infection Clinical Management and Follow-Up

There is no curative treatment for ZIKV infection. In both **Part A** and **Part B,** study sites should have plans for subjects to have access to clinical care and management of ZIKV infection based on recommendations by CDC, WHO, and/or site local authority. Subjects should continue to participate in VRC 705 follow-up visits while under care. Study staff must document all signs and symptoms of infection and all clinical care provided.

Any subject with a positive ZIKV result must be discontinued from receiving study product. In addition, pregnancy testing and pregnancy prevention counseling must be added to all study visits for female subjects of childbearing potential following a ZIKV diagnosis, as shown on Tables B and C in the Schedule of Evaluations.

In areas where there is an option, per PI discretion, it is acceptable for a ZIKV-infected study subject to co-enroll in a concurrent study of treatment or management of ZIKV infection to allow for optimal care of the subject. The IND Sponsor should be notified if co-enrollment occurs. Treatment procedures and co-enrollments will be documented in the study database and available to the Protocol Safety Review Team (PSRT) through study reports. With permission from the subject, the results of diagnostic testing and other evaluations conducted for this study may be shared with the clinician(s) providing the medical care to minimize the need for the subject to have extra blood draws or repeat testing.

4.3.5. Reporting of ZIKV Infections

All confirmed cases of ZIKV infection will be reported to the IND Sponsor through data entry in the database. Test results for DENV, CHIKV and hemorrhagic fever must be reported as an AE, according to the corresponding AE reporting period as noted in protocol Section 5.1.1. Sites must also comply with local regulatory requirements for reporting ZIKV infections and other reportable infections of interest, such as DENV and CHIKV, as applicable.

4.3.6. ZIKV Infection in Pregnant Women

Per Section 4.2.7, in case of pregnancy, subjects will be removed from the product administration schedule but may have limited clinic contacts and blood draws at the discretion of the site PI and IND Sponsor. Pregnant women will also be advised about reducing risks of becoming infected with ZIKV. However, if a pregnant woman becomes infected with ZIKV, she will be referred for care based on the site's prepared list of resources. All pregnancies that begin

during the study will be recorded. The site must contact the subject to learn the outcome of any pregnancy that begins during the study.

4.4. Concomitant Medications

Only routine medications should be entered in the database at the time of study randomization. All approved vaccinations for routine health care must be entered in the database throughout the study. Concomitant medications will be updated in the study database if there is an occurrence of an AE that requires expedited reporting or development of a new chronic medical condition that requires ongoing medical management. Otherwise, concomitant medications taken during the study, including those for DENV infection, must be recorded in the subject study file.

Vaccines during the Study: As stated above, subjects may receive routine vaccinations throughout the study as needed for standard healthcare practice. Product administrations must be scheduled such that:

- No inactivated vaccine is received within 2 weeks before or after each product administration
- No live attenuated vaccine is received within 4 weeks before or after each product administration

4.5. Criteria for Discontinuing Product Administrations or Subject Participation

Decisions to discontinue giving the second or third product administrations or to discontinue protocol participation for a subject will be made by the site PI or designee.

4.5.1. Discontinuation from Receiving Study Product

Subjects who receive at least one product administration are expected to continue with planned follow-up visits until the end of the study. If the second product administration is not given, then the subject should be discontinued from the third product administration.

A subject may be discontinued from getting study product for the following reasons:

- Pregnancy;
- Grade 3 AE assessed as related to study product (except that self-limited Grade 3 solicited reactogenicity does not require discontinuation of product administrations);
- Grade 4 AE assessed as related to study product;
- Immediate hypersensitivity reaction associated with study product;
- Confirmed ZIKV infection;
- Clinically significant intercurrent illness that is not expected to resolve before the next scheduled product administration;
- Treatment with systemic glucocorticoids (e.g., prednisone or other glucocorticoid) or other immunomodulators (other than nonsteroidal anti-inflammatory drugs [NSAIDs]), with the exception that study product administration may continue per site PI discretion if the next one occurs at least 2 weeks following completion of glucocorticoid treatment; or,

- The IND Sponsor and/or PI assess that it is not in the best interest of the subject to continue receiving study product.

4.5.2. Discontinuation from Protocol Participation

A subject may be discontinued from protocol participation for the following reasons:

- Subject voluntarily withdraws;
- Subject develops a medical condition that is a contraindication to continuing on study;
- The IND Sponsor or regulatory authorities stop the protocol; or,
- The IND Sponsor and/or PI assess that it is not in the best interest of the subject to continue participation or that the subject's compliance with the study is not sufficient.

4.6. Criteria for Pausing and Resuming the Study

The PI for each site, study team, and IND Sponsor will closely monitor and analyze study data as they become available and will make determinations regarding the presence and severity of AEs. Product administrations, new enrollments, and randomizations will be paused and the IND Sponsor will be promptly notified according to the following criteria:

- **One** (or more) subject experiences a **Serious Adverse Event (SAE)** assessed by the PI as related to study product.
- **Two** (or more) subjects experience the same **Grade 4 unsolicited AE** assessed by the PI as related to the study product.

Plan for Review of Pauses and Resuming Rules:

The IND Sponsor, with participation by the PSRT, will conduct the review and consult with the Data and Safety Monitoring Board (DSMB) to make the decision to resume, amend or close the study. As part of the pause review, the reviewers will also advise on whether the study needs to be paused again for any subsequent AEs of the same type.

Product administrations, new enrollments, and randomizations would resume only if review of the AEs that caused the pause result in a recommendation to permit further product administrations, enrollments, and randomizations. When indicated, safety data reports and changes in study status will be submitted to relevant regulatory authorities including the site IRB/EC in accordance with Section 5.5 and site institutional policy.

5. SAFETY AND ADVERSE EVENTS

5.1. Adverse Events

An adverse event (AE) is 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 use of study treatment, whether or not considered related to the study treatment. AEs will be graded according to the Table for Grading Severity of AEs (Appendix IV).

All AEs will be followed until they have resolved or are considered stable during the course of the study. If the event has a resolution date, this date must be recorded on the Adverse Event form, regardless of whether or not it falls within the AE reporting period.

5.1.1. AE Reporting Period

The following guidelines will be used to determine if an AE should be recorded in the database:

- Solicited AEs (i.e. reactogenicity parameters) will be recorded in the study database for 7 days after each product administration without the collection of their relationship to study product.
- Unsolicited AEs and their relationship to study product must be recorded in the study database immediately after the first product administration at Visit 02 through the one month visit that follows the last product administration. Therefore, the following rules apply:
  - If a subject receives all 3 study product administrations, then the AE Reporting Period for unsolicited AEs and their relationship to study product is immediately after Visit 02 through Visit 05.
  - If a subject **only** receives the first product administration at Visit 02 but not the second or third, then the AE Reporting Period for unsolicited AEs and their relationship to study product is immediately after Visit 02 through Visit 03.
  - If a subject receives the first and second product administrations at Visit 02 and Visit 03, respectively, but not the third, then the AE Reporting Period for unsolicited AEs and their relationship to study product is immediately after Visit 02 through Visit 04.
- Only SAEs (as defined in Section 5.2), new chronic medical conditions, and confirmed cases of DENV infection, diagnosed locally or by the PDL, are recorded as AEs through the last study visit.
- Confirmed cases of ZIKV infection are not recorded as an AE unless the infection meets the definition of a SAE. ZIKV infections must be recorded on the ZIKV Endpoints Form throughout the full duration of the study.

5.2. Serious Adverse Events

5.2.1. Serious Adverse Event Definition

The term “serious adverse event” (SAE) as defined in US 21 Code of Federal Regulations (CFR) 312.32 as follows: “an adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

“Life threatening” refers to an AE that, at occurrence, represented an immediate risk of death to the subject. An event that hypothetically may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

5.2.2. Reporting Serious Adverse Events to the IND Sponsor

AEs that meet the definition of a SAE must be reported from the time that the subject signs the informed consent/assent form through the last study visit by the study site and submitted on an expedited basis to the IND Sponsor, according to sponsor guidelines as follows:

- results in death;
- is life-threatening;
- results in persistent or significant disability/incapacity;
- requires unplanned inpatient hospitalization or prolongation of existing hospitalization;
- is a congenital anomaly/birth defect in the offspring of a study subject; or,
- is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Additionally, any event, regardless of severity, which in the judgment of a site PI represents a SAE, may be reported on an expedited basis.

Reporting to the IND Sponsor: Within 3 calendar days of site awareness of the SAE occurrence, the site PI or designee will communicate an initial SAE report to the IND Sponsor through the communication methods provided by VRC’s CRO. The site will remove personal identifying information about the subject from SAE case reports before submission to the IND Sponsor.

Any SAE entered into the study database will generate an automatic email notification to the IND Sponsor. A written event summary by the study site should be sent to the IND Sponsor within 7 calendar days and sooner, if possible, in case of death. Additional information should

be submitted as it becomes available. The IND Sponsor will use this information to comply with FDA regulations mandating notification of expedited SAEs.

5.2.3. IND Sponsor Reporting to the FDA

It is the responsibility of the IND Sponsor to make the determination of which SAEs are "serious and unexpected suspected adverse reactions" (SUSARs) as defined in 21 CFR 312.32.

- *Suspected adverse reaction* means any AE for which there is a reasonable possibility that the drug caused the AE.
- *Unexpected adverse event* means an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.

All SUSARs, as determined by the IND Sponsor, will be reported to the FDA as IND Safety Reports. All IND Safety Reports will be provided to all participating site PIs by the IND Sponsor and should be submitted to site local or national regulatory authorities as required.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in US 21 CFR 312.33.

5.2.4. Serious Adverse Event Reporting to the Data and Safety Monitoring Board

SAEs that occur during the study will be reported to the DSMB by the IND Sponsor or sponsor representative on a monthly basis. However, any SAE that is reported to the FDA as a IND Safety Report will be reported to the DSMB as soon as possible.

5.2.5. Serious Adverse Event Reporting to the Institutional Biosafety Committee

In keeping with Institutional Biosafety Committee (IBC) requirements, sites will follow their IBC reporting regulations per institutional policy.

5.3. Protocol Deviation

A Protocol Deviation is defined as any change, divergence, or departure from the IRB/EC-approved study procedures in a research protocol. This includes but is not limited to:

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

5.4. Unanticipated Problem

A serious Unanticipated Problem (UP) is defined as any incident, experience, or outcome that meets all three of the following criteria:

- unexpected in nature, severity, or frequency in relation to the research risks that are described in the protocol, informed consent, IB, other study documents or in consideration of the characteristics of the subject population being studied; **and**
- related to participation in the research; **and**

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Non-serious UP: An UP that is not an Adverse Event (UPnonAE) is 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 samples, or unaccounted-for study drug.

5.5. Reporting to Site IRBs/ECs and Relevant Regulatory Agencies

Each site PI is responsible for reporting study information to the site IRB/EC per the IRB/EC requirements for reporting and to other relevant regulatory authorities in accordance with their institutional and country requirements for reporting.

Site-specific data reports will be made available through the data management CRO to facilitate expedited and continuing review reporting requirements.

Only the IND Sponsor will submit reports to the FDA. Any IND Safety Report that is submitted to the FDA will also be provided to all sites, with instructions on whether or not any action needs to be taken. Investigators must maintain documentation of compliance with actions required for IND Safety Reports.

5.6. Data and Safety Monitoring Board

The PSRT (Section 8.9.1) will have the primary responsibility for the regularly scheduled oversight of safety data and SAE reviews. The NIAID DSMB will review cumulative study data at least twice per year or as often as recommended by the DSMB to evaluate safety, study conduct, and scientific validity and integrity of the trial and will be consulted if there is a study pause as required by Section 4.6.

The DSMB members will assess the timeliness, completeness, and accuracy of the data submitted to them for review and whether the data are sufficient for evaluation of the safety and welfare of study subjects. The DSMB Executive Secretary will be provided with a sealed copy of the randomization codes needed for the DSMB review of the safety data. The DSMB will also assess the performance of overall study operations and any other relevant issues, as necessary. Following each review, the DSMB will provide its recommendations to the IND Sponsor, including whether the study should continue without change, be modified, or be terminated.

In addition, SAEs will be reported to the DSMB as outlined in Section 5.2.4.

6. STATISTICAL CONSIDERATIONS AND SAMPLE ANALYSIS

6.1. Overview

This is a multicenter, randomized, study to evaluate the safety, immunogenicity, and efficacy of VRC-ZKADNA90-00-VP (ZIKVwt DNA vaccine) or placebo. The hypotheses are that the ZIKVwt DNA vaccine will be safe and will elicit a ZIKV-specific immune response. In **Part A**, the primary objective is to evaluate the safety and tolerability of the vaccine. In **Part B**, the primary objectives are to evaluate the safety, tolerability, and efficacy of the vaccine compared to placebo. In **Part A** and **Part B**, secondary and exploratory objectives relate to immunogenicity/durability of immune responses, incidence of subclinical and symptomatic ZIKV infection, and ZIKV viremia/viruria following infection.

6.2. Endpoints

6.2.1. Safety

Assessment of product safety will include clinical observation and monitoring of hematological and chemical parameters. Reactogenicity will be closely monitored for 7 days after each product administration and safety evaluated by clinical visits through the study duration of 32 or 96 weeks in **Part A** or **Part B**, respectively.

The following parameters will be assessed:

- Local reactogenicity signs and symptoms;
- Systemic reactogenicity signs and symptoms;
- Laboratory measures of safety;
- Adverse events;
- Serious adverse events, new chronic medical conditions, and confirmed cases of DENV; and,
- ZIKV infection events (**Part B only**).

6.2.2. Immunogenicity

The principal immunogenicity endpoints are 4 weeks after the last product administration compared to Day 0 as measured by neutralization assay. Exploratory immunogenicity endpoints are measured by neutralization assay, ELISA, and other research tests as described in Section 1.7.

6.2.3. Efficacy (Part B only)

The primary efficacy endpoint is the ZIKV incidence defined as virologically confirmed infection by PCR virus detection. The secondary efficacy endpoint is the incidence of subclinical virologic cases.

6.3. Sample Size and Accrual

6.3.1. Sample Size Considerations: Part A

Part A of the study targets healthy adults (age 18-35). Since the risk of GBS has been shown to increase with age, the study population excludes those who might be at higher perceived risk for GBS [54-56]. Ninety subjects will be randomized 1:1:1 to three vaccination arms. The sample size decision is based on the evaluation of vaccine safety and immunogenicity. Accrual up to 100 subjects is permitted if additional subjects are needed for safety and immunogenicity evaluations.

6.3.1.1. Power Calculations for Evaluation of Safety

The ability of the study to identify safety events can be expressed in terms of the probability of observing one or more event of interest (e.g., AEs) within each group assuming a range of underlying true event rates. With 30 subjects per group, assuming the true event rate of 0.3%, there is a probability of 8.6% to observe at least one event and a probability of 0.4% to observe more than one event (Table 2).

Table 2: Probability of Observing Safety Events within a Group (n=30)

True Event Rate (%)	Pr (0 event) (%)	Pr (more than one event) (%)
0.1	97.0	<0.1
0.3	91.4	0.4
0.5	86.0	1.0
1.0	74.0	3.6
3.0	40.1	22.7
5.0	21.5	44.6

Table 3 shows the 95% confidence intervals (CIs) of the true event rate based on the observed safety data. Calculations are done using exact binomial test. For a given arm with sample size n=30, if none of the subjects experience a safety event, the 95% CI has upper bound as 0.116.

Table 3: Two sided 95% CIs Based on Observed Rates of Safety Endpoints within a Group (n=30)

Observed event rate	95% CI	
	Lower bound	Upper bound
0/30	0	0.116
1/30	0.001	0.172
2/30	0.008	0.221
3/30	0.021	0.265
4/30	0.038	0.307
5/30	0.056	0.347

6.3.1.2. Power Calculations for Evaluation of Immunogenicity

The evaluation of immunogenicity includes the magnitude of the immune response as well as the positive response rate. The primary endpoint is the immune response measured by neutralization assay at 4 weeks after the last product administration. Table 2 provides the probability of observing zero or more than one positive responses within a group of size 30 and Table 3 provides the 95% CIs of the positive response rate in the vaccinated population. Neutralization assay data are close to being log-normally distribution. The magnitude of immune response due to the study vaccine can be evaluated by the fold change from baseline. Table 4 shows the power of detecting a range of fold changes, assuming normal distribution after log transformation with standard deviation=1, within a group of size 30. Table 5 presents the power of detecting between-arm differences over a range of effect sizes, assuming normal distribution after log transformation with common standard deviation. The calculations are done using t-tests in log scales. With 30 subjects per group, the study is capable of detecting with over 80% power the fold change of 0.75 and above within a group, and over 80% power the between-arm difference of 0.80 standard deviation and above in log scale.

Table 4: Power of Detecting a Range of Fold Changes from Baseline Immune Response

Fold change	Power (%)
0.25	22
0.50	57
0.75	84
1.00	96

Table 4 is based on assuming normal distribution after natural log transformation with standard deviation=1, by one sample two-sided t-test with type I error rate of 5%, within a group (n=30).

Table 5: Power of Detecting Between-Arm Difference over a Range of Effect Sizes

Effect size of between-arm difference	Power (%)
0.5	48
0.6	63
0.7	76
0.8	86
0.9	93

Table 5 is based on assuming normal distribution after log transformation, by two-sample two-sided t-test with type I error rate of 5% (n=30).

6.3.2. Sample Size Considerations: Part B

Part B of the study targets healthy adults and adolescents ages 15 to 35 years who reside in ZIKV endemic or potential endemic regions. This age range is considered to be the range of the highest reproductive potential and therefore, this age group will likely be the initial target for a successful ZIKV vaccine. Additionally, the risk of GBS has been shown to increase with age, so

this study population excludes those who might be at higher perceived risk for GBS [54-56]. Randomization at each study site will equally allocate subjects to vaccine or placebo schedules. The randomization plan does not include provisions for replacing subjects with incomplete product administration or visit schedules.

A total of 2400 subjects will be randomized 1:1 to receive either the study vaccine or placebo. The study sample size was determined primarily based on the evaluation of vaccine efficacy (VE). The study also has ample sample size for detecting AEs, therefore meeting the primary endpoints.

To detect a VE of 61%, the trial aims to achieve 90 cases of naturally acquired virologic ZIKV infection within 2 to 3 years. If it appears this target is unlikely to be met, the study may be expanded to achieve this target. Prior to the completion of randomization, the combined vaccine and placebo incidence rate of subclinical ZIKV cases will be calculated. At each site, the blinded site-specific baseline seropositivity rate may be calculated and used to adjust the needed sample size and to aid in allocation of enrollment slots. Both types of rates will be used to help decide if the enrollment should be extended to allow for the target to be achieved. For planning purposes, we will allow for a total sample size of up to 15,000. Such a sample size could achieve our target number of virologic ZIKV cases within 3 years, assuming full accrual within 12 months, even if the placebo incidence rate is as low as 0.50% and the seropositive rate is as high as 30% among enrollees.

Sample size will be re-evaluated prior to the end of the randomization period to estimate if we will achieve 90 cases of virologic ZIKV infection in 2 to 3 years. This calculation will explicitly take into account the accrual rate, the dropout rate, the baseline seropositive rate, and the incidence rate. Values for these rates will be based on within trial data augmented by other information (e.g., historical dropout rates in other studies, epidemiologic projections of incidence from other sources). If this calculation suggests the sample size of 2400 is inadequate to achieve 90 cases of virologic ZIKV infection in 2 to 3 years, the sample size may be increased.

Accrual may occur rapidly at more than one site. The data managers will carefully monitor study accrual and notify the sites and Protocol Chairs when completion of accrual is near.

6.3.2.1. Power Calculations for Evaluation of Safety

The goal of the safety evaluation for this study is to identify safety concerns associated with administration of the investigational vaccine. Two sample size calculations for safety are expressed in terms of two approaches, within group and comparing two groups.

The ability of the study to identify safety events may be expressed in terms of the probability of observing one or more event of interest (e.g., AEs) within each group assuming a range of underlying true event rates. With 1200 subjects per group and the true event rate of 0.3%, there is a probability of 97.3% to observe at least one event and a probability of 87.5% to observe more than one event (Table 6).

Safety event rates may vary considerably with the type of event considered. Safety will be evaluated within each arm and additionally stratified by baseline ZIKV status, pre-exposed or not.

Table 6: Probability of Observing Safety Events within a Group (n=1200)

True Event Rate (%)	Pr (0 event) (%)	Pr (more than one event) (%)
0.01	88.7	0.7
0.05	54.9	12.2
0.10	30.1	33.7
0.30	2.7	87.5
0.50	0.2	98.3

Table 7 provides the minimum detectable difference by two-sided chi-square test between the vaccine and placebo groups over a range of possible event rates and sample sizes as follows: 1200 samples per group, 960 samples per group to account for 20% early drop out, 480 and 240 samples per group for comparisons within a stratum defined by baseline ZIKV status.

Table 7: Minimum Detectable Difference in Event Rate Assuming Type I Two-Tail Error Rate of 5%

Sample size within each group (#)	Event rate (in placebo) (%)	Detectable with 80% power		Detectable with 90% power	
		Difference (%)	Event rate (in vaccine) (%)	Difference (%)	Event rate (in vaccine) (%)
1200	0.1	0.81	0.91	1.04	1.14
	0.5	1.19	1.69	1.46	1.96
	1.0	1.50	2.50	1.80	2.80
	5.0	2.80	7.80	3.29	8.29
	10.0	3.69	13.69	4.32	14.32
	25.0	5.11	30.11	5.93	30.93
960	0.1	0.98	1.08	1.26	1.36
	0.5	1.39	1.89	1.71	2.21
	1.0	1.73	2.73	2.09	3.09
	5.0	3.17	8.17	3.74	8.74
	10.0	4.16	14.16	4.88	14.88
	25.0	5.73	30.73	6.66	31.66
480	0.1	1.79	1.89	2.33	2.43
	0.5	2.30	2.80	2.88	3.38
	1.0	2.75	3.75	3.38	4.38
	5.0	4.72	9.72	5.60	10.60
	10.0	6.08	16.08	7.15	17.15
	25.0	8.20	33.20	9.55	34.55
240	0.1	3.38	3.48	4.43	4.53
	0.5	3.97	4.47	5.04	5.54
	1.0	4.54	5.54	5.65	6.65
	5.0	7.14	12.14	8.55	13.55
	10.0	8.98	18.98	10.61	20.61
	25.0	11.79	36.79	13.73	38.73

6.3.2.2. Power Calculations for Evaluation of Immunity

The evaluation of immunogenicity includes the magnitude of the immune response as well as the positive response rate. The primary endpoint is the immune response measured by neutralization assay at 4 weeks after the third product administration. Neutralization assay data are close to being log-normally distribution. Table 7 provides the minimum detectable between-group difference with respect to positive response rate. Table 8 presents the minimum detectable effect size of the between-group difference in log scale with respect to the magnitude of immune response by two-sided t-test. With 1200 subjects per group, the study is capable of detecting the between-group difference with 80% power if the mean of the between-group difference is 0.11 and the standard deviation is 1 on the log scale. If the standard deviation is 0.30, the study is capable of detecting a 0.03 between-group difference with 80% power and 1200 per group.

Table 8: Minimum Detectable Difference in the Magnitude of Immune Response (log transformed) between 2 Groups Assuming Type I Two-Tail Error Rate of 5%

Standard Deviation	Subjects within each group (#)	Minimum detectable effect size	
		With 80% power	With 90% power
1	1200	0.11	0.13
	960	0.13	0.15
	480	0.18	0.21
	240	0.26	0.30
0.30	1200	0.03	0.04
	960	0.04	0.04
	480	0.05	0.06
	240	0.08	0.09

6.3.2.3. Power Calculations for Evaluation of Efficacy

This trial is designed as an event driven study to test the null hypothesis that VE $\leq$ 20%. The efficacy endpoint will be evaluated once a fixed number of ZIKV cases have occurred. Table 9 provides the number of cases that are required to achieve 80% and 90% power for the test of the null hypothesis (VE $\leq$ 20%) for various assumed VEs using the R function binom.power. For this calculation, we note that conditional on the total number of cases, the probability a case comes from the vaccine group is equal to (1-VE)/(2-VE). Thus, the null probability that a case comes from the vaccine is given by (1-0.2)/(2-0.2) = 4/9. Simulations show that power from this conditional binomial calculation is an excellent approximation to the power from a Cox regression model which will be used for analysis. With ninety cases of virologic ZIKV infection, the study is capable of detecting a vaccine efficacy of 61% with 90% power. While these calculations assume there is no interim monitoring and the study will be monitored using an O'Brien-Fleming boundary for efficacy, such monitoring has a negligible impact on power.

Table 9: Number of Cases of Virologic ZIKV Infection Required to Achieve 80% or 90% Under Different Vaccine Efficacies by Conditional Binomial Test with Two-sided Type I Error Rate of 0.05 and Null VE ≤ 20%

Vaccine Efficacy	Cases of ZIKV infection for 80% power (#)	Cases of ZIKV infection for 90% power (#)
0.80	20	27
0.70	37	50
0.61	66	89
0.60	71	95
0.50	150	201

While the study is designed to achieve 90 cases of virologic ZIKV infection, the sample size required to achieve this goal will depend on the duration of the study and the yearly incidence rate in the placebo group. Table 10 provides the expected number of cases of virologic ZIKV infection with 2 or 3 years of follow-up from the start of accrual under different assumptions about the placebo yearly incidence rate while assuming a VE of 61% and a total sample size of 2400. For this calculation, we assume that the 2400 subjects are accrued within 6 months.

Table 10: Expected Number of Cases of Virologic ZIKV Infection within 2 and 3 Years of Trial Initiation under Different Assumed Yearly Incidence under Placebo with 2400 Subjects

Yearly Incidence of cases of ZIKV infection (under placebo)	Cases of ZIKV infection within 2 years (#)	Cases of ZIKV infection within 3 years (#)
0.005	14	23
0.010	29	45
0.020	57	91
0.030	86	136
0.040	114	181

Therefore, we see that if the placebo incidence rate is 3%, the target of 90 infections will take about 2 years to achieve. If the placebo incidence rate is 2%, the target of 90 infections will take about 3 years to achieve.

The annual incidence of virologic ZIKV cases is uncertain and may be lower than 2%. In addition, at ZIKV endemic sites, some enrollees in the study may have been pre-exposed to ZIKV and are therefore unlikely to become virologic ZIKV cases. To compensate for low incidence and/or baseline seropositive subjects, we may need to expand the sample size. Table 11 gives the expected number of virologic ZIKV cases by 2 or 3 years from a potentially expanded study that accounts for 0% to 30% seropositive enrollees at baseline over a range of annual incidence rates that can be as low as 0.25% under placebo. In these calculations, we assume baseline seropositives will not become infected with ZIKV and the incidence rate applies to the baseline seronegatives and a VE of 61%. We also assume that enrollment is completed within 12 months.

Table 11: Expected Number of Cases of Virologic ZIKV Infection among Seronegative Enrollees within 2 and 3 Years of Trial Initiation under Different Assumed Baseline Seropositive Rates, Yearly Incidence Rates under Placebo among Seronegatives, and Sample Sizes

Seropositive rate at baseline (%)	Total sample size (#)	Yearly incidence (under placebo)	Cases of ZIKV infections within 2 years (#)	Cases of ZIKV infections within 3 years (#)
0	7500	0.0100	78	130
	12500	0.0050	65	108
	15000	0.0050	78	130
	15000	0.0025	39	65
10	7500	0.0100	70	117
	12500	0.0050	58	97
	15000	0.0050	70	117
	15000	0.0025	35	58
	20000	0.0025	47	78
30	7500	0.0100	54	91
	12500	0.0050	45	76
	15000	0.0050	54	91
	15000	0.0250	27	45
	25000	0.0250	45	76

If the seropositive rate at baseline is no more than 30% and the yearly incidence for cases of virologic ZIKV infection is 0.005, i.e., 0.5% under placebo, then with VE of 61%, an expanded study of size 15000 reaches the targeted 90 cases of ZIKV infections within 3 years if enrollment is completed within 12 months.

6.4. Statistical Analysis

Study accrual is defined in this protocol as being randomized to a treatment group and receiving the first administration of study product. All accrued subjects will receive at least one product administration and therefore will provide some safety data. The safety population will include all enrolled subjects, summarized according to the actual vaccination dose received.

In **Part B**, all subjects will be tested for baseline ZIKV serostatus based on samples collected at Visit 02 prior to the first product administration. Since those with prior exposure to ZIKV may respond differently to the vaccine from those naïve subjects, safety, immunogenicity and efficacy will be analyzed within each stratum defined by baseline ZIKV status in addition to overall strata combined. **Part A** of the study is to be conducted at endemic or potentially endemic sites with baseline ZIKV serostatus tested, then safety and immunogenicity analyses will be similarly run by stratum in addition to overall strata combined.

Three types of analysis cohorts are defined. The Intent-to-treat (ITT) cohort will include all accrued subjects according to group assignment. The Per Protocol (PP) cohort will include all subjects receiving all planned vaccinations within window as assigned by the randomization schedule, and not experiencing any other major protocol deviations prior to the visit of

evaluation. The Modified intent-to-treat (mITT) analyses will include all accrued subjects who remain event-free one week after all planned product administration, where event is the primary efficacy event of a positive ZIKV PCR test result.

No multiple comparison adjustment will be employed for safety, immunogenicity, or efficacy analyses. Missing data will be primarily considered as missing completely at random in safety and immunogenicity analysis provided missing data is modest (e.g. <5-10%). For completeness, we will examine the missing data completely at random assumption and perform sensitivity analyses which weaken the missing completely at random assumption if the missing data is >10% or if the missing at random assumption is questionable. For efficacy, missing at random will be assumed and methods for handling missingness, such as multiple imputation and inverse propensity weighting, will be considered.

In general, descriptive statistics by vaccine group will be tabulated for all variables of interest, stratified by baseline ZIKV testing results. This will include point estimates (mean, geometric mean, median or proportions) and their respective 95% CI or percentile spread. Formal comparisons will use standard methods, contingency tables for categorical variables, t-tests or non-parametric analogs for comparing means or geometric means, logistic regression and analysis of covariance for model discrete and continuous variables respectively.

6.4.1. Baseline Demographics

Baseline characteristics including demographics and laboratory measurements will be summarized by vaccine group and stratum.

6.4.2. Safety Analysis

Reactogenicity: The number and percentage of subjects experiencing each type of reactogenicity sign or symptom will be tabulated by severity. For a given sign or symptom, each subject's reactogenicity will be counted once under the maximum severity for all assessments.

Adverse Events: AEs will be coded into Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentage of subjects experiencing each specific AE will be tabulated by severity and relationship to treatment. For the calculations in these tables, each subject's AE will be counted once under the maximum severity or strongest recorded causal relationship to treatment.

A complete listing of AEs for each subject will provide details including severity, relationship to treatment, onset, duration and outcome.

Safety Laboratory Values: Safety laboratory values will be summarized using shift tables to compare baseline and follow-up values. Shift tables will be analyzed using Generalize Estimating Equations to account for the longitudinal nature of these data. The mean change from baseline along with 95% CI at each time point measured in the study will be computed. Boxplots of safety laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile, with values smaller than the 1st quartile or larger than the 3rd quartiles plotted as outliers. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

6.4.3. Analysis of Immune Responses

Immunogenicity will be analyzed for a variety of cohorts defined above, and specified in the SAP (Statistical Analysis Plan). At minimum these may include ITT, PP, and mITT cohorts. Assay results will be examined to determine if their distributions should be analyzed as normal, lognormal, nominal or categorical. It may also be appropriate to dichotomize the data into "responders" and "non-responders". Immunogenicity data will be analyzed at each time point where such data is collected. Longitudinal methods will be used to estimate the nature and extent of immune response decay over time. Immunogenicity will be assessed by group. To account for preexisting immunogenicity due to prior ZIKV exposure, immunogenicity will also be assessed according to baseline serostatus as a secondary analysis.

6.4.4. Analysis of ZIKV Incidence

Efficacy evaluation with respect to ZIKV incidence will be performed in **Part B**. Incidence rates for ZIKV cases will be described by vaccine group and by baseline ZIKV stratum for each group. Results will be treated both as dichotomous (infection, no infection) and as a time to event (infection) variables. The primary analysis will be based on the time to case of virologic ZIKV infection, i.e., when a subject is positive for ZIKV based on a PCR test. The time to ZIKV case data, accounting for censoring, will be described using Kaplan-Meier curves and efficacy computed using a Cox proportional hazards model. VE will be estimated by the hazard ratio from the Cox proportional hazards model stratified by baseline ZIKV exposure status.

The primary efficacy analysis is a test of the null hypothesis (H0): the study vaccine has VE no more than 20% in preventing ZIKV infection, i.e., VE $\leq$ 20%, where ZIKV infection is defined as virologically confirmed infection by PCR virus detection. The alternative hypothesis is that VE > 20%. The criterion for success will be that a one-sided test of H0 has p-value $\leq$ 0.025. This primary analysis will be based on the mITT cohort stratified by baseline serostatus (prior exposed to ZIKV or not). If the null VE $\leq$ 20% is not rejected, an additional test of H0*: VE = 0 will be conducted using a one-sided type I error rate of 0.025.

The secondary efficacy analyses include the testing of this hypothesis over the two stratum combined. Another secondary analysis will test the above hypothesis H0, where ZIKV infection is defined as PCR virus detection irrespective of symptoms. The SAP will provide any necessary additional specificity and/or cohort definitions such as discussed at the beginning of Section 6.4.

6.4.5. Interim Analyses

Independent Safety Reviews:

The PSRT will review safety data routinely throughout the study. The study will utilize both electronic database features and reviews by designated safety review personnel to identify in a timely manner if any of the safety pause rules of the study are met. The DSMB will provide an independent safety review at scheduled intervals to coincide with their biannual meeting schedule.

Immunogenicity Reviews:

Part A: The data in **Part A** will be used in an ongoing manner to help select the regimen to be used in **Part B**.

Part B: An interim analysis of immunogenicity data may be performed after the NAb assays up to and including Week 12 have been completed on a subset of subjects. Reports will be provided to the Protocol Chairs and other key investigators solely for the purpose of informing future trial-related decisions in a timely manner. The results will remain confidential and should in no way influence the conduct of the VRC 705 trial in terms of early termination or later safety or immunogenicity endpoint assessments.

Efficacy Reviews (Part B only):

The final efficacy analysis will occur when the total number of virologic ZIKV cases in **Part B** of the study reaches 90. Interim efficacy analysis will be performed when the total number of virologic ZIKV cases in the mITT cohort reaches 30 and 60. To preserve a one-sided type I error rate of 2.5%, the Lan-DeMets spending function will be adopted. The Lan-DeMets analog of the O'Brien-Fleming boundary, or equivalently, the nominal significance of 0.0001, 0.006, and 0.023 will be used in the two interim analyses and the final analysis, respectively, for declaring efficacy. These tests will be of the null H0: VE $\leq$ 20%.

To examine for harm (i.e., a greater rate of ZIKV cases in the vaccine arm) a 95% nominal CI for the hazard ratio will be calculated. A guideline for stopping is met if this CI excludes 0 in the direction of harm. Harm will be monitored after 15, 30, 45, 60, and 75 cases have accrued. Harm will be monitored using both the ITT and mITT cohorts.

Incidence Reviews (Part B only):

The study will be regularly monitored using the combined (blinded) incidence rates for ZIKV disease and for ZIKV infections. These rates will be monitored at each site and over all sites combined. Such monitoring will allow for enrollment to be expanded or curtailed at different sites.

The trial will periodically evaluate the expected time to achieve 90 cases of virologic ZIKV disease and may be stopped for lack of feasibility if this expected time is deemed excessive.

6.4.6. Randomization of Treatment Assignments and Unblinding Criteria

Randomizations will be done online using an electronic randomization system. The randomization code will be prepared by the Protocol Statistician and included in the enrollment module for the trial. The randomization code will link to the treatment assignment. The electronic data system will assign each subject a randomization code after eligibility has been confirmed in the system.

In **Part A**, randomization will be performed with 1:1:1 allocation to the three vaccination arms at each study site. In **Part B**, randomization will be performed with 1:1 allocation to the ZIKV DNA vaccine and placebo at each study site.

Part A will be open-label and no unblinding will be needed. In **Part B**, the injections will be prepared by an unblinded site pharmacist, designee, or otherwise qualified personnel who will not be involved in any subject assessments and who will not discuss randomizations with blinded study staff. The subjects, the study personnel who perform product administrations and

assessments, data entry personnel at the sites, and laboratory personnel performing immunologic assays will be blinded to the treatment assignment of all product administrations. Product assignments will be provided to the site PI at completion of the study per the Study Blinding Plan for communication to the study subjects. The DSMB may receive data in aggregate and presented by treatment group, but without the treatment group identified. The DSMB may be unblinded to individual study treatment assignments, as needed, to adequately assess safety issues.

The IND Sponsor intends to unblind treatment assignments for **Part B** of the study once 90 cases of ZIKV infection are detected. The DSMB will be consulted prior to unblinding.

If necessary, the site PI or designee and Protocol Chair may agree that an event, such as management of an AE or pregnancy, requires emergency unblinding of an individual subject's assignment. If early unblinding occurs for any reason, it will be documented as a protocol deviation. The Protocol Statistician, the site IRB/EC (as required), and the DSMB will be notified that an early unblinding has occurred and provided with a statement explaining the medical necessity for the early unblinding.

7. PHARMACY PROCEDURES

7.1. Study Products

The study products are prepared under cGMP by the VRC Pilot Plant and must meet lot release specifications prior to release for use in the clinical study. This study includes one investigational vaccine and one placebo (and diluent) as follows:

- VRC-ZKADNA090-00-VP (ZIKVwt DNA vaccine) is supplied as a 3-mL glass vial containing a clear, colorless, isotonic, PBS-buffered (pH 7.2) sterile solution. Each vial contains a total fill volume of either 1.2 mL (+/- 0.1 mL) or 1.5 mL (+/- 0.1 mL), at a concentration of 4 mg/mL. Vials are intended for single use only and do not contain a preservative. Vials must not be refrozen or reused after thawing.
- VRC-PBSPLA043-00-VP, phosphate buffered saline (PBS), placebo control and diluent, is a clear, colorless, sterile solution at pH 7.2 aseptically filled to a volume of 1.2 mL or 1.5 mL in 3-mL glass vials. Vials are intended for single use only and do not contain a preservative. Vials must not be refrozen or reused after thawing.

Both study products are clear, colorless solutions and there is no difference in appearance. Study products may only be shipped to the site pharmacy per IND Sponsor approval. Vials are shipped using appropriate shipping configurations.

7.2. Study Product Presentation, Stability and Storage

7.2.1. Labels

At the time of study product delivery to the pharmacy, labels on study products, VRC-ZKADNA090-00-VP and VRC-PBSPLA043-00-VP, will have specific product information (e.g., product description, VRC product number, lot number, fill volume, concentration, fill date,

storage condition). Labels will contain an Investigational Use Statement ("Limited by Federal Law to Investigational Use") and manufacturer information.

7.2.2. Storage

VRC-ZKADNA090-00-VP: Vaccine vials will be shipped to the study pharmacy at the recommended temperature range using appropriate shipping configurations. Vaccine vials will be stored until use at the target temperature of -35°C to -15°C in a qualified, continuously-monitored, temperature-controlled freezer. As freezer temperatures may fluctuate, a temperature range of -45°C to -10°C is acceptable based upon historic stability data from studies of similar products. Storage below -45ºC is not permitted because of stopper temperature limitation.

If deviations in storage temperature occur from the normal allowance for the pharmacy freezer, the site pharmacist or designee must quarantine affected product(s) and report the storage temperature excursion within 48 hours to the site PI and IND Sponsor. The excursion must be evaluated and investigated, and action must be taken to restore and maintain the desired temperature limits. Pending the outcome of the investigation, the IND Sponsor will notify the site pharmacist or designee if clinical use of the affected product is acceptable and the affected product may be removed from quarantine.

VRC-PBSPLA043-00-VP: Vials of PBS are stored until use at the target temperature of -35°C to -15°C in a qualified, continuously monitored, temperature-controlled freezer. As freezer temperatures may fluctuate, a temperature range of -45°C to -10°C is acceptable based upon historic stability data from studies of similar products.

7.2.3. Stability

Study product vials must equilibrate to room temperature after removal from the freezer for use. Keep filled syringes at room temperature and out of direct sunlight until the product is administered. Vaccine and placebo are stable for up to 8 hours after being removed from the freezer and therefore, must be administered within those 8 hours.

7.3. Preparation of Study Products for Administration

Refer to the IB for information on study products preparation and use. Refer to the group assignment for the study subject to select the proper product type.

Label all **Part A** syringes with "VRC 705 Study Product for IM administration" and all **Part B** syringes with "VRC 705 Study Product or Placebo for IM administration." In addition, all **Part A** and **Part B** labels must include the subject identifier, group number (Part A only), treatment number (Part B only), time removed from freezer, time of expiration, and preparer's initials and date.

Site staff should practice universal precautions and dispose of syringes and the needle-free device disposable components in keeping with the site policy and practices.

7.4. Study Product Administration

All injections will be administered using PharmaJet. The PharmaJet syringes are single use, auto-disabling, disposable containers designed to hold 0.5 mL fluid volume. Reference the instructions in the IB to fill the PharmaJet syringes.

Additional product administration instructions are listed in protocol Section 4.2.6.1.

7.5. Study Product Accountability

7.5.1. Documentation

Each study site will be responsible for maintaining an accurate record of the treatment codes, inventory and an accountability record of the investigational study product supplies for this study.

7.5.2. Disposition

Empty vials and the unused portion of a vial must be discarded on the day of use in a biohazard container that will be incinerated or autoclaved in accordance with site policy. Any unopened vials that remain at the end of the study will be discarded at the discretion of the IND Sponsor in accordance with policies that apply to investigational products. Partially used vials or expired prepared doses cannot be administered to other subjects nor used for *in vitro* experimental studies and will be discarded as indicated above.

8. HUMAN SUBJECTS PROTECTION

This research will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidances, and all applicable regulatory requirements.

8.1. Institutional Review Board/Ethics Committee

A copy of the protocol, proposed consent/assent forms, and any proposed advertising material must be submitted to the site IRB/EC for review and approval.

The site PI must submit and, where necessary, obtain approval from the IRB/EC for subsequent protocol amendments and changes to the consent/assent forms. The site PI is responsible for ensuring proper IRB/EC notification of protocol deviations or SAEs occurring at the site and other AE reports received from the VRC, in accordance with the protocol and local IRB/EC and regulatory policies. The PI will be responsible for obtaining annual IRB/EC approval/renewal throughout the duration of the protocol. Documentation of the IRB/EC approval and FWA number must be provided to the IND Sponsor.

8.2. Institutional Biosafety Committee

Institutional Biosafety Committees (IBCs) are the cornerstone of institutional oversight of recombinant DNA research. Research with recombinant or synthetic (or both) nucleic acid molecules that is performed at or sponsored by an institution that receives any NIH funding for such research is required to adhere to IBC guidelines. Documentation of IBC approval for the study must be provided to the IND Sponsor.

8.3. Subject Recruitment and Enrollment

Subjects for this study will be recruited by the sites in accordance with their IRB/EC standards for recruitment practices.

8.3.1. Participation of Children

This study meets the US Department of Health and Human Services regulations (45 CFR 46, Subpart D, 401-409) for inclusion and protections for children/minors who participate in research. Healthy minors can participate in research studies considered as "not greater than minimal risk" and can participate in research with greater than minimal risk only when it presents the prospect of direct benefit to the individual minor or is likely to yield generalizable knowledge about the child's condition and meets the criteria in 45 CFR 46, Subpart D.

Participation in this study will not provide any benefits directly to individual minors; however, this study is likely to yield generalizable knowledge that is considered necessary for the development of a ZIKV vaccine regimen that would provide durable immune responses and be protective. In accordance to the 45 CFR 46, Subpart D, research involving greater than minimal risk and no prospect of direct benefit to the individual subjects should be scientifically sound and significant, and have the following conditions met to be approved:

a. The risk represents a minor increase over minimal risk;

b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

d. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

The conditions listed above have been considered and incorporated in this protocol for minimization of risk to adolescents who may participate.

Children ages 14 years and younger are not eligible to participate in this clinical trial because this study is designed for study product evaluation in adults and adolescents of reproductive age. If the product is assessed as safe and immunogenic, other protocols designed for younger children may be conducted in the future.

8.3.2. Participation of Site Employees

Each study site will follow institutional policies related to study participation of site employees. Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the subject's employment or work situation.

8.4. Informed Consent and Assent

Before a subject's participation in the protocol, it is the site PI or designee's responsibility to ensure that written informed consent is obtained from the subject (and parent/guardian if applicable) after adequate explanation of the purpose, methods, anticipated benefits, and potential hazards of the protocol. The ICF must be signed and personally dated by the subject, and by the person who conducted the informed consent discussion. The subject must also record the time of his or her signature.

As of protocol version 4.0, the Sponsor-required witness, for the sole purpose of verifying and attesting to the subject's signing of the informed consent/assent form, is no longer required.

However, an impartial witness, defined as a person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent/assent process, and who reads the informed consent/assent form and any other written information supplied to the subject, is required if a subject or subject's legally acceptable representative (LAR) is unable to read. In the case of an impartial witness, he/she should be present during the entire informed consent/assent discussion. After the written informed consent/assent form and any other written information provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or subject's LAR has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent/assent form, the witness should sign and personally date the form. By signing the consent/assent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR, and that informed consent/assent was freely given by the subject or subject's

LAR. Sites must also follow local regulations for the use of a LAR or witness to consent subjects who are unable to read, as needed.

Per site regulations for adolescents, sites may use an assent form in conjunction with an ICF signed by the parent/guardian, or sites can use only a consent form, provided that both the subject and the parent/guardian consent is obtained on the form.

The acquisition of informed consent/assent must be documented in the subject's records, as required by 45 CFR 46.117. The original signed consent/assent form must be retained by the site with the subject's study records and a copy of the signed form must be provided to the subject.

The provided template study informed consent and assent forms (Appendix I**)** will be used to guide development of the site-specific forms. Only IRB/EC-approved informed consent/assent forms will be used to consent and re-consent subjects for study participation.

All changes made to the templates by the site must be approved by the IND Sponsor before submission to the respective IRB/EC and other regulatory authorities.

Study sites that need to conduct the informed consent/assent process in more than one language will follow the practices required by their IRB/EC for translation and approval of the consent(s). All translated and English back-translated consent/assent documents must be provided to the IND Sponsor.

8.5. Subject Confidentiality

Site investigators must ensure that the subject's anonymity is maintained and will ensure that no information identifying the subject will be released to any unauthorized party. Subjects will not be identified in any reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. Medical records will be made available for review when required by authorized agencies and regulatory authorities only under the guidelines set by the US Federal Privacy Act and by relevant country-specific regulatory authorities. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. Subject confidentiality will not be violated. Stored study research samples will be labeled by a code (such as a number) that only the study team can link to the subject. The requirement to maintain subject confidentiality and inform subjects about review of study-related records is included in the study informed consent documents.

8.6. Risks and Benefits

8.6.1. Risks of the ZIKVwt DNA vaccine

The investigational ZIKV DNA vaccine, VRC-ZKADNA085-00-VP, which is similar to the ZIKVwt DNA vaccine, VRC-ZKADNA090-00-VP, is being tested in a Phase 1 study, VRC 319. As of July 24, 2018, 80 subjects have enrolled into VRC 319 and received at least 2 or 3 injections of the ZIKV DNA vaccine by needle and syringe; 45 subjects have enrolled into VRC 320 and received at least one injection of the ZIKVwt DNA vaccine by PharmaJet. Both products have been well tolerated based on early findings, as reported in Section 1.3.

Subjects may exhibit general signs and symptoms associated with administration of a vaccine including fever, chills, rash, aches and pains, nausea, headache, dizziness and fatigue. These

side effects will be monitored, but are generally short term, mild to moderate in severity and usually do not require treatment.

In previous VRC DNA vaccine studies, placebo and vaccine recipients were noted to have occasional asymptomatic and self-limited changes in laboratory tests such as temporary decrease in white blood cell count. Urticaria has been reported as an AE possibly related to DNA vaccines.

Neurological complications including GBS have been reported in people diagnosed with ZIKV infection. While GBS has not been observed with other DNA vaccines or vaccines developed against other flaviviruses, we cannot rule out all concern for GBS. The cause of GBS associated with ZIKV disease is still under investigation. To minimize the risk of GBS, which has been shown to increase with age, the study population is limited to healthy adults and adolescents 15-35 years of age.

It is unknown if the study vaccine will affect how subjects respond to a future ZIKV infection or ZIKV vaccine that may be available in the future. There may be side effects from the study products, which may be serious or life threatening, that we do not yet know about.

8.6.2. Risks of Administration with a Needle-Free Injection Device

Investigational DNA vaccines administered via Biojector have been associated with mild skin lesions (0.5-1.0 cm diameter) at the injection site. In these cases, a small scab formed within 1-2 weeks and then came off after a few days. The skin healed without treatment within a few weeks.

Potential side effects resulting from IM injection by needle-free devices include stinging, arm discomfort, redness of the skin, mild bruising, or a small laceration at the injection sites.

Product administrations with PharmaJet have been ongoing in VRC 705 Part A and B since March 29, 2017 and July 19, 2017, respectively. As of July 24, 2018, 0.54% of injections have involved a device malfunction. The malfunctions have included the syringe breaking and in rare cases, study product spraying during product administration. This has resulted in some subjects not receiving the full dose of study product. However, no study subjects experienced adverse events due to these malfunctions. The potential for spray due to syringe breakage has led to the determination that staff administering the PharmaJet device and subjects receiving the product administration must both wear safety glasses during the procedure.

8.6.3. Other Risks

Blood drawing may cause pain, bruising, fainting, and, rarely, infection at the site where the blood is taken.

We do not know the possible effects of the study vaccine on the fetus or nursing infant. Therefore, females of childbearing potential will be tested for pregnancy prior to each product administration.

It is possible that the standard medical tests performed as part of this research protocol will result in new diagnoses. Depending on the medical findings and consequences of being provided with the new medical information about health status, the study subject may view this aspect of study participation as either a risk or a benefit. Any such information will be shared and discussed

with the subject and, if requested by the subject, will be forwarded to the subject's primary health care provider for further workup and management.

8.6.4. Benefits

Study subjects will not receive direct health benefit from study participation. This protocol is not designed to provide treatment for any condition. Others may benefit from knowledge gained in this study that may aid in the development of a ZIKV vaccine. The investigational vaccine is not expected to provide protection from ZIKV infection.

8.7. Plan for Use and Storage of Biological Samples

To be eligible for this protocol, subjects must be willing to allow stored specimens to be used in the future for studying infectious diseases, immune function, vaccine responses and other medical conditions. Samples from vaccinated individuals will be critical to development of new antibody detection assays for ZIKV diagnosis and for characterization of antibody as well as T- and B-cell responses. These samples will be required for case-control analysis of breakthrough ZIKV infections in vaccine versus placebo recipients.

If tests performed at a study site show evidence of any acute or chronic condition, subjects will be informed of the results and advised to seek appropriate medical care for the condition. Research tests performed at a research laboratory are not for diagnostic purposes and results will generally not be available to the study site or study subject.

8.7.1. Use of Samples, Specimens and Data

Samples, specimens and data collected under this protocol may be used by the protocol team to conduct protocol-related safety and immune response evaluations, exploratory laboratory evaluations related to ZIKV infection, exploratory laboratory evaluations related to vaccine or infectious disease research in general, and for research assay validation.

8.7.2. Storage and Tracking of Blood Samples and Other Specimens

All of the stored study research samples are labeled by a code that only the site can link to the subject. Coded (de-identified) samples are stored at secure facilities with limited access including NVITAL, Gaithersburg, MD, and VRC Laboratories in Bethesda, MD or other approved CRO facilities. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data. Samples will be tracked in GlobalTrace^{SM} and may be transferred to other approved databases as needed for analysis.

8.7.3. Disposition of Samples, Specimens and Data at Completion of the Protocol

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. Regulatory approval through the proper human subjects protection agency will be sought prior to any sharing of samples that constitutes human subjects research. The research use of stored, unlinked or unidentified samples may be exempt from the need for IRB/EC review and approval. When appropriate, exemption may be obtained through the proper regulatory procedures.

At the time of protocol termination, samples will remain in the contracted central repository, the NVITAL facility, or VRC laboratories; or, after IRB/EC approval, samples may be transferred to

another repository. Regulatory oversight of the stored samples and data may be transferred to a stored samples protocol as part of the IRB/EC-approved termination plan. Data will be archived by the IND Sponsor in compliance with requirements for retention of research records, or after the IRB/EC and the IND Sponsor approval, it may be either destroyed or transferred to another repository.

8.7.4. Loss or Destruction of Samples, Specimens or Data

The NIH Intramural Protocol Deviation definition related to loss of or destruction of samples or data will be followed. Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that compromises the scientific integrity of the study will be reported to the site IRB/EC in accordance with institutional policies. The site PI will also notify the site IRB/EC if the decision is made to destroy the remaining samples.

8.8. Compensation

Compensation for time and inconvenience of study participation will be provided to subjects in accordance with the site-specific IRB/EC approved plan. This includes scheduled visits and unscheduled visits, such as for evaluation of possible ZIKV infection.

Suggested compensation rates per visit include: $25-$75 for clinic visits, $50-$100 for product administration visits, $5-$20 for phone contacts, $15-$25 for returning the completed diary card, and $10-$100 bonus for completion of the study as appropriate. Site-specific compensation rates will be determined based on site SOPs and regional rates of compensation for participation in clinical trials for healthy subjects.

8.9. Safety Monitoring

8.9.1. Protocol Safety Review Team

Each site PI is responsible for ensuring daily review of the site's clinical safety data as it becomes available. The PSRT includes the Protocol Chairs and IND Sponsor Medical Officers. The summary study safety data reports will be reviewed weekly and the PSRT will meet as needed (generally weekly) by teleconference to review any safety issues requiring discussion from initiation of the study until 4 weeks after all subjects have received their last product administration. After that, the PSRT will meet monthly (or more/less frequently as needed) until 4 weeks after all subjects have completed the last study visit to be certain that the investigational vaccine has an acceptable safety profile. The PSRT will be notified and convened to review any study pauses.

8.9.2. Data and Safety Monitoring Board

As described in Section 4.6, the DSMB will be consulted to make a decision to resume, amend or close the study following a safety pause. As described in Section 5.6, the DSMB will review safety data at least twice per year at their regularly scheduled meetings and will have access to the randomization code.

9. ADMINISTRATION AND LEGAL OBLIGATIONS

9.1. Protocol Initiation, Amendments and Termination

Each site must receive IRB/EC approval, approval from local country regulatory agencies, as needed, and approval of IND Sponsor before initiating the study at the site.

Protocol amendments must be made only with the prior approval of the IND Sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. All amendments will also be submitted to the site IRBs/ECs and other regulatory authorities as needed for approval.

The VRC, NIAID, NIH, FDA and other regulatory authorities reserve the right to terminate the study. Each site PI will notify the respective site IRB/EC of the study termination in writing and provide documentation to the IND Sponsor.

9.2. Study Documentation and Study Records Retention

The site PI will maintain a list of appropriately qualified persons to whom trial duties have been delegated. The site PI is responsible for ensuring that staff maintains a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the IND Sponsor, site IRB/EC, designated CRO monitor and/or applicable regulatory authorities. Elements include but are not limited to:

- Subject files containing completed informed consent/assent forms and copies of supporting source documentation, and,
- Study files containing the protocol with all amendments, the IB, and copies of all correspondence with the IRB/EC and local regulatory authorities, when applicable.

In addition, all original source documentation must be maintained and readily available.

The CRO is responsible for ensuring that records and documents pertaining to the conduct of this study, including CRFs, source documents, consent/assent forms, laboratory test results, and study product inventory records, are managed per US requirements. The CRO will request financial disclosure forms from applicable site personnel at the beginning of the trial. Financial disclosure information must be kept current and must be promptly updated if any relevant changes occur during the period of time the investigator participated in the study and for one year following study participation. According to the FDA, study records must be retained for 2 years after the marketing application is approved for the product; or, if an application is not approved for the product, until 2 years after shipment and delivery of the product for investigational use is discontinued. Study sites are also responsible for ensuring local regulations for record retention are followed, as applicable. The IND Sponsor may authorize transfer or destruction of study records and none will be destroyed without prior authorization.

9.3. Data Collection, Data Sharing, and Protocol Monitoring

9.3.1. Data Collection

Clinical research data will be collected and recorded by the study sites in a timely fashion in a secure electronic web-based clinical data management system. Immunological testing on

collected, coded blood samples may be performed in batches at central laboratories. Extracted data without subject identifiers will be sent to the statisticians for statistical analysis as needed. The final study database and statistical evaluations will be transferred to the IND Sponsor at study completion.

9.3.2. Data Sharing

Data generated in this study will be shared as de-identified data in the government-funded public repository, www.ClinicalTrials.gov. Data may be shared prior to publication at approved public presentations or for collaborative development and will be shared at the time of publication or within 1 year thereafter.

9.3.3. Source Documents

Each participating study site will maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) GCP, regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in the NIAID-sponsored study, each site will permit authorized representatives of the VRC, NIAID, designated CROs and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of original documents and data records include but are not limited to: medical records, diary cards, laboratory reports, pharmacy records and other research records for the clinical trial.

9.3.4. Protocol Monitoring

The IND Sponsor, VRC, or their authorized representatives are responsible for ensuring integrity of study data and compliance with the protocol. Routine data monitoring and protocol compliance will be performed by the site investigators and study coordinator on an ongoing basis in accordance with the IND Sponsor's monitoring plan. Site investigators will allow the study monitors, IND Sponsor, the US FDA, and/or other regulatory authorities (if requested) to inspect study documents or pertinent clinic records for confirmation of study data.

9.4. Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are readily understood.

9.5. Policy Regarding Research-Related Injuries

Each study site will provide immediate medical care for any injury resulting from participation in this research. In general, the VRC, NIAID, NIH, or US Government will not provide long-term medical care or financial compensation for research-related injuries.

9.6. Multi-Site Management

The IND Sponsor is responsible for overall study management. Assistance in managing the study is being provided by specific CROs.

Each study site that enrolls study subjects will have a site PI. A PI is defined as an individual who actually conducts a clinical investigation at a study site and under whose immediate direction the test article is administered to subjects. The site PIs have parallel roles at their respective institutions in conducting the study at their site in compliance with all applicable regulations and good clinical practices.

Publication of any study related information is governed by VRC, NIAID, NIH policies. Specifically, neither the CROs nor site personnel may submit for public presentation any meeting abstract or manuscripts without prior review by VRC.

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APPENDIX I: TEMPLATE INFORMED CONSENT FORM AND ASSENT FORM

The sample informed consent and assent forms are provided to guide development of a site-specific documents. Only IRB/EC-approved forms will be used to consent/assent subjects for study participation.

Template: Study Informed Consent Form – Part A

STUDY TITLE: VRC 705: A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

INTRODUCTION

We invite you to take part in a research study conducted at the [**insert site name**].

The study is sponsored by the National Institutes of Health (NIH) in Bethesda, MD, US. You can choose if you want to take part in this study or not. There is no penalty or loss of benefits for choosing not to take part in this study. Please ask questions and discuss this study with anyone you want. Take as much time as you need to decide. You will be given a copy of this consent form.

SCREENING

Before you can take part in this experimental Zika DNA vaccine study, your health will be checked so we can decide if you qualify. You will need to sign this consent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health. We will ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy. During screening, we will collect some blood to store for research. We will review the test results with you and tell you if the results show that you are eligible to join the study.

PURPOSE OF THIS STUDY

This is a research study of an experimental vaccine against Zika virus infection. "Experimental" means that the study vaccine has not been approved by the US Food and Drug Administration (FDA). The FDA allows this vaccine to be used for research purposes only. This vaccine has been given to people in a Phase 1 study. We do not know if the vaccine works. The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study immune responses to the vaccine including cells that may recognize and fight Zika virus. This study will take place in areas where Zika outbreaks are happening or may happen.

BACKGROUND ON ZIKA VIRUS

Zika virus was discovered in 1947. It is named after the Zika Forest in Uganda where it was found. Until recently, Zika infections happened in parts of Africa and Asia. Recent outbreaks have been reported in North, Central and South America, the Caribbean, the Pacific Islands, and Africa.

Zika is passed from human to human by infected mosquitos. Zika can also be passed through sex from a person who has Zika to his or her partners, and from a mother to her child during pregnancy. Zika infection causes symptoms that are usually mild and may include fever, rash, joint pain, and conjunctivitis (red eyes). Many times, there are no symptoms at all, so many

people do not know that they have been infected. Symptoms usually last from 2 to 7 days. People usually don't get sick enough to go to the hospital, and they very rarely die. A person who has been infected once is not likely to get Zika infection again.

Recently, some cases of microcephaly (abnormally small head and brain) and other birth defects were found in babies that were born to mothers who had a Zika infection. Some people who had Zika infection also had rare cases of a severe muscle weakness called Guillain-Barré syndrome. We do not know why some people who get Zika infection develop Guillain-Barré syndrome. Most people who develop Guillain-Barré syndrome recover over time. If you have ever had this condition, you will not qualify for this study.

There is currently no cure for or vaccine to prevent Zika infection.

We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

STUDY PLAN

This study has 2 parts, Part A and Part B. Part A of the study has 3 groups with a total of 90 people. We will test the vaccine at doses of 4 milligrams (mg) or 8 mg split into either 2 or 4 injections. Part A will last for 32 weeks or about 8 months. Part B of the study has 2 groups with a total of about 2400 people. We will test the vaccine in comparison to the placebo, which is a salt-water solution that has no vaccine in it. Part B will last for 96 weeks or about 24 months.

By signing this form, you are agreeing to take part in **Part A**. The plan for Part A is below:

VRC 705 – Part A							
Group	**Subjects**	**Dose**	**Number of Injections**	**Location of Injections**	**Product Administration**		
					Day 0	**Week 4**	**Week 8**
1	30	4 mg	2	each arm	vaccine	vaccine	vaccine
2	30	4 mg	4	each arm and each leg	vaccine	vaccine	vaccine
3	30	8 mg	4	each arm and each leg	vaccine	vaccine	vaccine
Total	**90**	Study product is given into the muscle by needle-free injection device.					

STUDY PRODUCT

The study product being tested in this study is VRC-ZKADNA090-00-VP, which is called the 'Zika DNA vaccine' or 'Zika vaccine'. The Zika vaccine was developed by the Vaccine Research Center (VRC) at the US NIH. It was made at the VRC Pilot Plant in Frederick, Maryland, US

Vaccines are given to help the body fight off an infection. When you get a dose of this vaccine, it should cause your body to make a small amount of Zika protein. Your body may use this protein to build an immune response against Zika.

There is no Zika virus in this vaccine. You cannot get Zika infection from this vaccine.

You should not expect this experimental Zika vaccine to protect you from Zika infection. You must take steps to protect yourself if you think you might be exposed to Zika in your environment. You should avoid mosquitos, use mosquito repellant, wear long sleeves and pants, and use bed nets at night. If you have any side effects that seem like Zika infection (including fever, rash, eye pain, red eyes, muscle aches, headache, or joint pain) while on the study, tell the study team right away so we can check you as soon as possible.

ELIGIBILITY

You may qualify to take part in this study if:

- you are between 18 [or **insert site-specific age that applies to adults]** and 35 years of age,
- you agree not to become pregnant for at least 12 weeks after you get the last product administration, which is about 5 months after the study begins,
- you have physical exam and blood test results that meet study requirements, and
- you do not have any serious medical problems as determined by your screening.

STUDY PROCEDURES

About 90 people will take part in Part A of this study. If you agree to join Part A, you will be assigned to one of the three study groups by chance (like flipping a coin). Once you are on the study, you will know which group you are in.

You will get a total of 3 product administrations. A product administration will be given at 3 separate visits that are each about 4 weeks apart. Depending on which study group you are in, you will get either 2 or 4 injections at each product administration visit. We will give all injections using the needle-free injection device called the PharmaJet Stratis® Needle Free Jet Injector (PharmaJet). In all study groups, PharmaJet injections will be given into the deltoid muscle on the arms. In some study groups, PharmaJet injections will also be given into the muscle on the upper thighs.

PharmaJet injects the vaccine into your body without using a needle. Instead of a needle, PharmaJet uses high pressure to push the vaccine through your skin into the muscle. Even though there is no needle, it may still cause pain. Needle-free devices have been used to give vaccines and other medications since the 1940s. This device has been cleared by the FDA for giving vaccine injections into the muscle. Studies have shown that some people who get injections with PharmaJet have more local reactions at the injection site than people who get injections with needle and syringe. However, the local reactions were mild.

If you are a female who is able to get pregnant, you will be given a pregnancy test before you get each product administration. The test must show that you are not pregnant before we can give you the study product.

We will watch you for at least 15 minutes after you get each full dose of study product, which is after you get all 2 or 4 injections.

We will ask you to complete a diary card for 7 days after each product administration. You will use the diary card to write down your highest temperature each day and any side effects that you feel. You will also need to look at the injection sites each day and write down how it looks and any side effects that you see. We will give you a thermometer and a measuring device to do this. We will ask you to review your diary card with us about a week later.

The clinic staff is available to you by phone 24 hours a day to report any unexpected side effects. If you have any concerning side effects or if you feel sick, you should tell the clinic right away. We may ask you to come into the clinic for an examination before your next scheduled visit. It is very important that you follow the instructions we give you.

Follow-Up Visits

You will be in the study for about 8 months after you get the first product administration. You will have about 11 clinic visits and 3 telephone contacts. Each clinic visit will last about [**insert site standard length of clinic visit**].

At each visit, we will ask you about any health changes or problems. We will ask how you are feeling and if you have taken any medications. At scheduled study visits, we will draw about 4 to 11 tubes of blood from you, depending on the visit. If any of your test results show a health problem, we will tell you about it as soon as possible. You might need to have extra clinic visits and laboratory tests if you have health changes that we need to check.

Experimental vaccine studies like this one follow a set schedule. The study schedule for your visits allows some flexibility, but it is important that you work with the staff to follow the set schedule as much as possible. You should try to not miss any visits.

Sample Collection for Zika Diagnosis

At any time during the study, if you think you have Zika infection, you must contact our clinic right away. We will ask you to come in for a clinical examination and we may collect blood and urine so that we can test you for Zika infection. If you have a rash or another sign or symptom of illness that could possibly be a Zika infection, we may take a photograph of the affected area with your permission. These photographs will not identify you in any way and will only be used by the study team to evaluate your illness. We may also test for other infections that have symptoms similar to Zika infection.

These samples will be shipped to either the Primary Diagnostic Laboratory at the University of Washington (Seattle, WA, US) or the Diagnostic and Reference Laboratory Arbovirus Diseases Branch, Centers for Disease Control and Prevention (CDC), Fort Collins, CO, US for testing.

We will tell you the results of your test(s) as soon as possible but it may take several weeks to get the results. It is very important that you get tested for Zika infection at our clinic **only** and that you do not get tested elsewhere unless it is necessary for your health, for example, while traveling.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time during the study. There is no penalty or loss of benefits for choosing to leave the study at any time.

MONITORING OF THE STUDY

This study will be monitored by a group of physicians and scientists associated with the US NIH. This group will review the study information and will pay close attention to any reactions that people have to the study product.

STORED SAMPLES

We will collect blood and other bodily fluids such as urine from you during this study. We will keep these samples to study your immune response to the study product and for future research to learn more about Zika, vaccines, the immune system or other related medical conditions. The urgency of the Zika epidemic has accelerated the development of Zika tests and assays. Samples from study subjects may be an important part in the development of new assays to diagnose and to study Zika infections. No genetic research (deoxyribonucleic acid [DNA] testing) will be done on these samples.

[**Add as required per local/national regulations**]: Research samples will be shipped to the Fisher BioServices (Germantown, MD, US) storage facility. Research samples may be stored for up to 20 years. Stored samples may be sent for testing by any of the following laboratories:

- VRC/NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL; Rockville, MD, US)
- NIAID Laboratory of Infectious Diseases (LID; Bethesda, MD, US)
- Battelle, Biomedical Research Center (West Jefferson, OH, US)
- Z-Quick/University of Miami Life Science and Technology Park (Miami, FL, US)
- Blood Systems Research Institute (BSRI, San Francisco, CA, US)
- PaxVax (San Diego, CA, US)

As new tests are developed, additional laboratories may use your stored samples for testing. These laboratories are unknown at this time.

Results from the research done with your stored samples are not for diagnostic purposes or medical care. Therefore, the results will not be part of your medical record.

Labeling of Stored Samples: Your stored samples will be labeled by a special code or number that only the study team can link to you. Any identifying information about you, like your name or date of birth, will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

Future Studies: In the future, other researchers at NIH or outside of NIH may wish to study your stored samples. When the study team shares your samples, they will be marked with a code. Your samples will not have any information on them that could identify you. Some information about you, such as your gender, age, health history, or ethnicity may be shared. Any future research done with your samples will be done in a way that protects the rights and privacy of study subjects.

Your stored samples will be used only for research and will not be sold. The research done with your samples may be used to develop new products in the future but you will not get payment for these products.

HUMAN DATA SHARING

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

You may stop participating in this study at any time and withdraw permission for your individual data, specimens, and health information to be used for additional or future research. You may ask to have your research data destroyed. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

POSSIBLE STUDY RISKS

***Possible* risks from the injections:** Temporary stinging, pain, redness, soreness, itchiness, swelling, or bruising. Injections given with the needle-free device have been shown to cause a small cut at the injection site. A small scab may form within 1 to 2 weeks after the injection is given. There is a very small chance of infection.

There is also a small chance that the needle-free device could not work properly. As of July 2018, 0.54% of VRC 705 injections involved a PharmaJet device malfunction. This includes the syringe breaking and study product spraying during administration. No study subjects were harmed because of these malfunctions. However, because there is the possibility of a malfunction, we ask that you wear safety glasses while we give you the injections.

***Possible* risks of blood drawing:** Pain, bleeding, bruising, feeling lightheaded, or fainting, and rarely, infection at the site where blood is taken.

***Possible* risks from any vaccine:** Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired or unwell. Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after an injection and typically last 1 to 3 days. Medicines, such as acetaminophen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction with symptoms such as hives, trouble breathing, or sudden weakness may happen shortly after any vaccination. This is called “anaphylaxis” and may be life-threatening. While you are waiting in the clinic after the injections, we will monitor you for anaphylaxis. Treatment for anaphylaxis will be given right away if it happens.

***Possible* risks of DNA vaccines:** Temporary drop in white blood cell count, sore arm, skin rash or hives, some people get a small red bump and then a scab for a few days where the injection is given. The NIH has tested many similar vaccines made by the VRC and these vaccines were found to be safe and well-tolerated. We expect this vaccine to be like the ones tested before.

***Possible* risks of the Zika DNA vaccine:** As of July 2018, this Zika vaccine has been tested in 45 subjects in the Phase 1 study, VRC 320. So far, the most common complaints after injection

by PharmaJet are mild or moderate headache and feeling tired or unwell, and mild pain at the injection site.

A very similar Zika vaccine has been tested in 80 subjects in the Phase 1 study, VRC 319. As of July 2018, that experimental vaccine was found to be safe for additional studies in humans. So far, the most common complaints after injection by needle and syringe have been mild pain at the injection site, and mild or moderate headache, muscle aches and feeling tired or unwell.

This Zika vaccine does not contain Zika virus. Guillain-Barré syndrome has not been seen with similar vaccines or vaccines made against similar viruses. We do not know if there is a risk of Guillain-Barré syndrome from the study vaccine. However, we have to be very cautious and observant with a Zika vaccine. This is because natural Zika infection seems to be associated with Guillain-Barré syndrome and we don't know how Zika might cause Guillain-Barré syndrome. You should tell the study team if you develop weakness or tingling in your arms or any other unusual symptoms.

***Possible* risks during Pregnancy:** We do not know if getting the study product will affect a fetus. Therefore, women and adolescents who can get pregnant must agree to use an effective method of birth control starting at least 21 days before getting the first product administration until 12 weeks after the last product administration. We will discuss effective birth control methods with you. If you are pregnant or want to become pregnant in the next 20 weeks, you cannot participate.

During the study, if you think you might be pregnant, you must tell the clinic staff right away. If you are pregnant, you will not get any more study product. We will give you resources you can use to learn about protecting yourself from getting Zika infection. You will be asked to continue with some follow-up visits. We will ask you about the outcome of the pregnancy.

Unknown risks: We do not know if the study product will affect how you respond to any future Zika infection or Zika vaccine that you may get in the future. There may be side effects from the study product, even serious or life threatening ones, that we do not yet know about. We will tell you if we learn about any important new findings or serious side effects of the vaccine during the study that may change your mind about your willingness to continue participation.

You may not donate blood while taking part in this study. You may not donate blood for one year after the date of your last product administration.

POSSIBLE BENEFITS

This study is not designed to benefit you or to protect you from Zika infection. You and others may benefit in the future from the information that we learn from the study.

COSTS OF PARTICIPATION

There are no costs to you for taking part in this study. You or your health insurance will have to pay for all medical costs for medical care that you get outside of this study. It is possible that you may have some costs that are not covered by the study compensation we give you.

COMPENSATION TO YOU FOR TAKING PART IN THE STUDY

You will be compensated [**insert site IRB/EC-approved amount**] for taking part in this study as follows: [**insert site plan**]. Total compensation will be based on the number of study visits you attend and the number of product administrations you get [or **insert site plan**].

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

The study doctor can take you out of this study without your consent if*:*

- continuing in the study could hurt you,
- you do not follow study instructions or keep your appointments, or
- the study is stopped by the US NIH, FDA, or regulatory authorities.

If you agree to take part in this study, it is important for you to keep all of your appointments. However, if you do not want to stay in the study, you can leave at any time. You will not lose any benefits that you would have had if you had not joined the study.

If you get at least one product administration, we will ask you to continue with your planned follow-up visits until the end of the study. It is important that we continue to check your health even if you do not get the second or third product administrations.

ALTERNATIVES

This study is not designed to treat or prevent any disease. You may choose not to take part.

CONFIDENTIALITY

[**Site/country-specific information on confidentiality may be added to this section**.]

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

Results of US NIH-supported research studies may also be reported in medical journals, on the internet or at scientific meetings. These reports will not have information that can identify you.

In most cases, the US NIH will not release any information about your research participation without your written permission. However, if you sign a release of information form, for example, for an insurance company, the insurance company gets information from your medical record. This information might affect (either positively or negatively) if the insurance company sells insurance to you.

POLICY REGARDING RESEARCH-RELATED INJURIES

The study site will provide immediate medical care for any injury resulting from you being in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the US NIH or the US Federal Government. However, you have the right to seek legal action if you think that your injury has a good reason for such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research subject, or about any research-related injury, call the Principal Investigator [**insert site PI information**]. You may also call the Study Coordinator [**insert site SC information]** or the Patient Representative at [**insert site Patient Representative, as applicable**]

Please keep a copy of this form in case you want to read it again.

SUBJECT CONSENT

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. All my questions have been answered to my satisfaction. I consent to take part in this study.

Subject Name (print):	Date and Time:
Signature:	

Investigator Name (print):	Date:
Signature:	

Template: Study Informed Consent Form – Part B

STUDY TITLE: VRC 705: A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

INTRODUCTION

We invite you to take part in a research study conducted at the [**insert site name**].

The study is sponsored by the National Institutes of Health (NIH) in Bethesda, MD, US. You can choose if you want to take part in this study or not. There is no penalty or loss of benefits for choosing not to take part in this study. Please ask questions and discuss this study with anyone you want. Take as much time as you need to decide. You will be given a copy of this consent form.

SCREENING

Before you can take part in this experimental Zika DNA vaccine study, your health will be checked so we can decide if you qualify. You will need to sign this consent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health. We will ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy. During screening, we will collect some blood to store for research. We will review the test results with you and tell you if the results show that you are eligible to join the study.

PURPOSE OF THIS STUDY

This is a research study of an experimental vaccine against Zika virus infection. "Experimental" means that the study vaccine has not been approved by the US Food and Drug Administration (FDA). The FDA allows this vaccine to be used for research purposes only. This vaccine has been given to people in a Phase 1 study. We do not know if the vaccine works. The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study immune responses to the vaccine including cells that may recognize and fight Zika virus. This study will take place in areas where Zika outbreaks are happening or may happen.

BACKGROUND ON ZIKA VIRUS

Zika virus was discovered in 1947. It is named after the Zika Forest in Uganda where it was found. Until recently, Zika infections happened in parts of Africa and Asia. Recent outbreaks have been reported in North, Central and South America, the Caribbean, the Pacific Islands, and Africa.

Zika is passed from human to human by infected mosquitos. Zika can also be passed through sex from a person who has Zika to his or her partners, and from a mother to her child during pregnancy. Zika infection causes symptoms that are usually mild and may include fever, rash, joint pain, and conjunctivitis (red eyes). Many times, there are no symptoms at all, so many

people do not know that they have been infected. Symptoms usually last from 2 to 7 days. People usually don't get sick enough to go to the hospital, and they very rarely die. A person who has been infected once is not likely to get Zika infection again.

Recently, some cases of microcephaly (abnormally small head and brain) and other birth defects were found in babies that were born to mothers who had a Zika infection. Some people who had Zika infection also had rare cases of a severe muscle weakness called Guillain-Barré syndrome. We do not know why some people who get Zika infection develop Guillain-Barré syndrome. Most people who develop Guillain-Barré syndrome recover over time. If you have ever had this condition, you will not qualify for this study.

There is currently no cure for or vaccine to prevent Zika infection.

We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

STUDY PLAN

This study has 2 parts, Part A and Part B. Part A of the study has 3 groups with a total of 90 people. We are testing the vaccine at doses of 4 milligrams (mg) or 8 mg split into either 2 or 4 injections. Part A will last for 32 weeks or about 8 months. Part B of the study has 2 groups with a total of about 2400. We will test the vaccine in comparison to the placebo, which is a salt-water solution that has no vaccine in it. Part B will last for 96 weeks or about 24 months.

By signing this form, you are agreeing to take part in **Part B**. The plan for Part B is below:

VRC 705 – Part B							
Group	**Subjects**	**Dose**	**Number of Injections**	**Location of Injections**	**Product Administration**		
					Day 0	**Week 4**	**Week 8**
4	1200	4 mg	2	both arms	vaccine	vaccine	vaccine
5	1200	0	2	both arms	placebo	placebo	placebo
Total	**2400**	Study products are given into the muscle by needle-free injection device.					

STUDY PRODUCTS

There are two study products in Part B of this study, the Zika vaccine and the salt water solution (or placebo). Half of the people in the study will get the vaccine and half will get the placebo.

1. Vaccine: In this study, the vaccine being tested is VRC-ZKADNA090-00-VP, which is called the 'Zika DNA vaccine' or 'Zika vaccine'. The Zika vaccine was developed by the Vaccine Research Center (VRC) at the US NIH. It was made at the VRC Pilot Plant in Frederick, Maryland, US.

Vaccines are given to help the body fight off an infection. When you get a dose of this vaccine, it should cause your body to make a small amount of Zika protein. Your body may use this protein to build an immune response against Zika.

There is no Zika virus in this vaccine. You cannot get Zika infection from this vaccine.

You should not expect this experimental Zika vaccine to protect you from Zika infection. You must take steps to protect yourself if you think you might be exposed to Zika in your environment. You should avoid mosquitos, use mosquito repellant, wear long sleeves and pants, and use bed nets at night. If you have any side effects that seem like Zika infection (including fever, rash, eye pain, red eyes, muscle aches, headache, or joint pain) while on the study, tell the study team right away so we can check you as soon as possible.

2. Placebo: The placebo in this study is a sterile salt water solution made for injection into people. It has no vaccine in it. We use the placebo as a control for the vaccine, so we can compare to the vaccine and see how it works.

ELIGIBILITY

You may qualify to take part in this study if:

- you are between [**insert site-specific age that applies]** and 35 years of age,
- you agree not to become pregnant for at least 12 weeks after you get the last product administration, which is about 5 months after the study begins,
- you have physical exam and blood test results that meet study requirements, and
- you do not have any serious medical problems as determined by your screening.

STUDY PROCEDURES

About 2400 people will take part in Part B of this study. If you agree to join Part B, you will be assigned to one of the two study groups by chance (like flipping a coin). You and the clinic staff will not know which study product you are getting until after the study is over.

You will get a total of 3 product administrations. A product administration will be given at 3 separate visits that are each about 4 weeks apart. You will get 2 injections at each product administration visit. We will give all injections using the needle-free injection device called the PharmaJet Stratis® Needle Free Jet Injector (PharmaJet). PharmaJet injections will be given into the deltoid muscle on each arm. In special cases, PharmaJet injections may also be given into the muscle on the upper thigh.

PharmaJet injects the vaccine into your body without using a needle. Instead of a needle, PharmaJet uses high pressure to push the vaccine through your skin into the muscle. Even though there is no needle, it may still cause pain. Needle-free devices have been used to give vaccines and other medications since the 1940s. This device has been cleared by the FDA for giving vaccine injections into the muscle. Studies have shown that some people who get injections with PharmaJet have more local reactions at the injection site than people who get injections with needle and syringe. However, the local reactions were mild.

If you are a female who is able to get pregnant, you will be given a pregnancy test before you get each product administration. The test must show that you are not pregnant before we can give you the study product.

We will watch you for at least 15 minutes after you get each full dose of study product, which is after you get both injections.

We will ask you to complete a diary card for 7 days after each product administration. You will use the diary card to write down your highest temperature each day and any side effects that you feel. You will also need to look at the injection sites each day and write down how it looks and any side effects that you see. We will give you a thermometer and a measuring device to do this. We will ask you to review your diary card with us about a week later.

The clinic staff is available to you by phone 24 hours a day to report any unexpected side effects. If you have any concerning side effects or if you feel sick, you should tell the clinic right away. We may ask you to come into the clinic for an examination before your next scheduled visit. It is very important that you follow the instructions we give you.

Follow-Up Visits

You will be in the study for about 2 years after you get the first product administration. You will have about 19 to 25 clinic visits and 3 telephone contacts. Each clinic visit will last about [**insert site standard length of clinic visit**].

At each visit, we will ask you about any health changes or problems. We will ask how you are feeling and if you have taken any medications. At scheduled study visits, we will draw about 2 to 9 tubes of blood from you, depending on the visit. If any of your test results show a health problem, we will tell you about it as soon as possible. You might need to have extra clinic visits and laboratory tests if you have health changes that we need to check.

Experimental vaccine studies like this one follow a set schedule. The study schedule for your visits allows some flexibility, but it is important that you work with the staff to follow the set schedule as much as possible. You should try to not miss any visits.

Sample Collection for Zika Diagnosis

At any time during the study, if you think you have Zika infection, you must contact our clinic right away. We will ask you to come in for a clinical examination and we may collect blood, and urine so that we can test you for Zika infection. If you have a rash or another sign or symptom of illness that could possibly be a Zika infection, we may take a photograph of the affected area with your permission. These photographs will not identify you in any way and will only be used by the study team to evaluate your illness. We may also test for other infections that have symptoms similar to Zika infection.

These samples will be shipped to either the Primary Diagnostic Laboratory at the University of Washington (Seattle, WA, US) or the Diagnostic and Reference Laboratory Arbovirus Diseases Branch, Centers for Disease Control and Prevention (CDC), Fort Collins, CO, US for testing.

We will tell you the results of your test(s) as soon as possible but it may take several weeks to get the results. It is very important that you get tested for Zika infection at our clinic **only** and that you do not get tested elsewhere unless it is necessary for your health, for example, while traveling.

Sample Collection for Zika Research

Many people who have Zika infection do not feel sick even when there is virus in their blood, urine, or other bodily fluids. As part of this study, we will collect blood samples from you about once a month for the first year and then every two months for the whole study (which is 96 weeks) so we can test for Zika infection. The sample collection plans may change if you get Zika infection. We will collect these samples for research purposes only.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time during the study. There is no penalty or loss of benefits for choosing to leave the study at any time.

MONITORING OF THE STUDY

This study will be monitored by a group of physicians and scientists associated with the US NIH. This group will review the study information and will pay close attention to any reactions that people have to the study products.

STORED SAMPLES

We will collect blood and other bodily fluids such as urine from you during this study. We will keep these samples to study your immune response to the study product and for future research to learn more about Zika, vaccines, the immune system or other related medical conditions. The urgency of the Zika epidemic has accelerated the development of Zika tests and assays. Samples from study subjects may be an important part in the development of new assays to diagnose and to study Zika infections. No genetic research (deoxyribonucleic acid [DNA] testing) will be done on these samples.

[**Add as required per local/national regulations**]: Research samples will be shipped to the Fisher BioServices (Germantown, MD, US) storage facility. Research samples may be stored for up to 20 years. Stored samples may be sent for testing by any of the following laboratories:

- VRC/NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL; Rockville, MD, US)
- NIAID Laboratory of Infectious Diseases (LID; Bethesda, MD, US)
- Battelle, Biomedical Research Center (West Jefferson, OH, US)
- Z-Quick/University of Miami Life Science and Technology Park (Miami, FL, US)
- Blood Systems Research Institute (BSRI, San Francisco, CA, US)
- PaxVax (San Diego, CA, US)

As new tests are developed, additional laboratories may use your stored samples for testing. These laboratories are unknown at this time.

Results from the research done with your stored samples are not for diagnostic purposes or medical care. Therefore, the results will not be part of your medical record.

Labeling of Stored Samples: Your stored samples will be labeled by a special code or number that only the study team can link to you. Any identifying information about you, like your name or date of birth, will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

Future Studies: In the future, other researchers at NIH or outside of NIH may wish to study your stored samples. When the study team shares your samples, they will be marked with a code. Your samples will not have any information on them that could identify you. Some information about you, such as your gender, age, health history, or ethnicity may be shared. Any future research done with your samples will be done in a way that protects the rights and privacy of study subjects.

Your stored samples will be used only for research and will not be sold. The research done with your samples may be used to develop new products in the future but you will not get payment for these products.

HUMAN DATA SHARING

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

You may stop participating in this study at any time and withdraw permission for your individual data, specimens, and health information to be used for additional or future research. You may ask to have your research data destroyed. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

POSSIBLE STUDY RISKS

Possible **risks from the injections:** Temporary stinging, pain, redness, soreness, itchiness, swelling, or bruising. Injections given with the needle-free device have been shown to cause a small cut at the injection site. A small scab may form within 1 to 2 weeks after the injection is given. There is a very small chance of infection.

There is also a small chance that the needle-free device could not work properly. As of July 2018, 0.54% of VRC 705 injections involved a PharmaJet device malfunction. This includes the syringe breaking and study product spraying during administration. No study subjects were harmed because of these malfunctions. However, because there is the possibility of a malfunction, we ask that you wear safety glasses while we give you the injections.

Possible **risks of blood drawing:** Pain, bleeding, bruising, feeling lightheaded, or fainting, and rarely, infection at the site where blood is taken.

Possible **risks from any vaccine:** Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired or unwell. Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after an injection and typically last 1 to 3 days. Medicines, such as acetaminophen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction with symptoms such as hives, trouble breathing, or sudden weakness may happen shortly after any vaccination. This is called “anaphylaxis” and

may be life-threatening. While you are waiting in the clinic after the injections, we will monitor you for anaphylaxis. Treatment for anaphylaxis will be given right away if it happens.

***Possible* risks of DNA vaccines:** Temporary drop in white blood cell count, sore arm, skin rash or hives, some people get a small red bump and then a scab for a few days where the injection is given. The NIH has tested many similar vaccines made by the VRC and these vaccines were found to be safe and well-tolerated. We expect this vaccine to be like the ones tested before.

***Possible* risks of the Zika DNA vaccine:** As of July 2018, this Zika vaccine has been tested in 45 subjects in the Phase 1 study, VRC 320. The most common complaints after injection by PharmaJet are mild or moderate headache and feeling tired or unwell, and mild pain at the injection site.

A very similar Zika vaccine has been tested in 80 subjects in the Phase 1 study, VRC 319. As of July 2018, that experimental vaccine was found to be safe for additional studies in humans. So far, the most common complaints after injection by needle and syringe have been mild pain at the injection site, and mild or moderate headache, muscle aches and feeling tired or unwell.

This Zika vaccine does not contain Zika virus. Guillain-Barré syndrome has not been seen with similar vaccines or vaccines made against similar viruses. We do not know if there is a risk of Guillain-Barré syndrome from the study vaccine. However, we have to be very cautious and observant with a Zika vaccine. This is because natural Zika infection seems to be associated with Guillain-Barré syndrome and we don't know how Zika might cause Guillain-Barré syndrome. You should tell the study team if you develop weakness or tingling in your arms or legs or any other unusual symptoms.

***Possible* risks during Pregnancy:** We do not know if getting the study products will affect a fetus. Therefore, women and adolescents who can get pregnant must agree to use an effective method of birth control starting at least 21 days before getting the first product administration until 12 weeks after the last product administration. We will discuss effective birth control methods with you. If you are pregnant or want to become pregnant in the next 20 weeks, you cannot participate.

During the study, if you think you might be pregnant, you must tell the clinic staff right away. If you are pregnant, you will not get any more study product. We will give you resources you can use to learn about protecting yourself from getting Zika infection. You will be asked to continue with some follow-up visits. We will ask you about the outcome of the pregnancy.

Unknown risks: We do not know if the study product will affect how you respond to any future Zika infection or Zika vaccine that you may get in the future. There may be side effects from the study products, even serious or life threatening ones, that we do not yet know about. We will tell you if we learn about any important new findings or serious side effects of the vaccine during the study that may change your mind about your willingness to continue participation.

You may not donate blood while taking part in this study. You may not donate blood for one year after the date of your last product administration.

POSSIBLE BENEFITS

This study is not designed to benefit you or to protect you from Zika infection. You and others may benefit in the future from the information that we learn from the study.

COSTS OF PARTICIPATION

There are no costs to you for taking part in this study. You or your health insurance will have to pay for all medical costs for medical care that you get outside of this study. It is possible that you may have some costs that are not covered by the study compensation we give you.

COMPENSATION TO YOU FOR TAKING PART IN THE STUDY

You will be compensated [**insert site IRB/EC-approved amount**] for taking part in this study as follows: [**insert site plan**]. Total compensation will be based on the number of study visits you attend and the number of product administrations you get [or **insert site plan**].

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

The study doctor can take you out of this study without your consent if:

- continuing in the study could hurt you,
- you do not follow study instructions or keep your appointments, or
- the study is stopped by the US NIH, FDA, or regulatory authorities.

If you agree to take part in this study, it is important for you to keep all of your appointments. However, if you do not want to stay in the study, you can leave at any time. You will not lose any benefits that you would have had if you had not joined the study.

If you get at least one product administration, we will ask you to continue with your planned follow-up visits until the end of the study. It is important that we continue to check your health even if you do not get the second or third product administrations.

ALTERNATIVES

This study is not designed to treat or prevent any disease. You may choose not to take part.

CONFIDENTIALITY

[**Site/country-specific information on confidentiality may be added to this section**.]

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

Results of US NIH-supported research studies may also be reported in medical journals, on the internet or at scientific meetings. These reports will not have information that can identify you.

In most cases, the US NIH will not release any information about your research participation without your written permission. However, if you sign a release of information form, for example, for an insurance company, the insurance company gets information from your medical record. This information might affect (either positively or negatively) if the insurance company sells insurance to you.

POLICY REGARDING RESEARCH-RELATED INJURIES

The study site will provide immediate medical care for any injury resulting from you being in research here. In general, no long-term medical care or financial compensation for research-

related injuries will be provided by the US NIH or the US Federal Government. However, you have the right to seek legal action if you think that your injury has a good reason for such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research subject, or about any research-related injury, call the Principal Investigator [**insert site PI information**]. You may also call the Study Coordinator [**insert site SC information]** or the Patient Representative at [**insert site Patient Representative, as applicable**]

Please keep a copy of this form in case you want to read it again.

SUBJECT CONSENT

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. All my questions have been answered to my satisfaction. I consent to take part in this study.

Subject Name (print):	Date and Time:
Signature:	

PARENT/GUARDIAN CONSENT

I/we have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. All my/our questions have been answered to my/our satisfaction. I/we hereby give permission for my child to take part in this study.

Parent/Guardian (1) *permission for minor patient, if applicable* (print):	Date:
Signature:	
Parent/Guardian (2, if applicable per site/country regulations) *permission for minor patient, if applicable* (print):	Date:
Signature:	

Investigator Name (print):	Date:
Signature:	

Template: Study Assent Form – Part B

STUDY TITLE: VRC 705: A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

INTRODUCTION

We invite you to take part in a research study conducted at the [**insert site name**].

The study is sponsored by the National Institutes of Health (NIH) in Bethesda, MD, US. You can choose if you want to take part in this study or not. There is no penalty or loss of benefits for choosing not to take part in this study. Please ask questions and discuss this study with anyone you want. Take as much time as you need to decide. You will be given a copy of this assent form.

SCREENING

Before you can take part in this experimental Zika DNA vaccine study, your health will be checked so we can decide if you qualify. You will need to sign this assent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health. We will ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy. During screening, we will collect some blood to store for research. We will review the test results with you and tell you if the results show that you are eligible to join the study.

PURPOSE OF THIS STUDY

This is a research study of an experimental vaccine against Zika virus infection. "Experimental" means that the study vaccine has not been approved by the US Food and Drug Administration (FDA). The FDA allows this vaccine to be used for research purposes only. This vaccine has been given to people in a Phase 1 study. We do not know if the vaccine works. The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study immune responses to the vaccine including cells that may recognize and fight Zika virus. This study will take place in areas where Zika outbreaks are happening or may happen.

BACKGROUND ON ZIKA VIRUS

Zika virus was discovered in 1947. It is named after the Zika Forest in Uganda where it was found. Until recently, Zika infections happened in parts of Africa and Asia. Recent outbreaks have been reported in North, Central and South America, the Caribbean, the Pacific Islands, and Africa.

Zika is passed from human to human by infected mosquitos. Zika can also be passed through sex from a person who has Zika to his or her partners, and from a mother to her child during pregnancy. Zika infection causes symptoms that are usually mild and may include fever, rash, joint pain, and conjunctivitis (red eyes). Many times, there are no symptoms at all, so many

people do not know that they have been infected. Symptoms usually last from 2 to 7 days. People usually don't get sick enough to go to the hospital, and they very rarely die. A person who has been infected once is not likely to get Zika infection again.

Recently, some cases of microcephaly (abnormally small head and brain) and other birth defects were found in babies that were born to mothers who had a Zika infection. Some people who had Zika infection also had rare cases of a severe muscle weakness called Guillain-Barré syndrome. We do not know why some people who get Zika infection develop Guillain-Barré syndrome. Most people who develop Guillain-Barré syndrome recover over time. If you have ever had this condition, you will not qualify for this study.

There is currently no cure for or vaccine to prevent Zika infection.

We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

STUDY PLAN

This study has 2 parts, Part A and Part B. Part A of the study has 3 groups with a total of 90 people. We will test the vaccine at doses of 4 milligrams (mg) or 8 mg split into either 2 or 4 injections. Part A will last for 32 weeks or about 8 months. Part B of the study has 2 groups with a total of about 2400 people. We will test the vaccine in comparison to the placebo, which is a salt-water solution that has no vaccine in it. Part B will last for 96 weeks or about 24 months.

By signing this form, you are agreeing to take part in **Part B**. The plan for Part B is below:

VRC 705 – Part B							
Group	**Subjects**	**Dose**	**Number of Injections**	**Location of Injections**	**Product Administration**		
					Day 0	**Week 4**	**Week 8**
4	1200	4 mg	2	both arms	vaccine	vaccine	vaccine
5	1200	0	2	both arms	placebo	placebo	placebo
Total	**2400**	Study products are given into the muscle by needle-free injection device.					

STUDY PRODUCTS

There are two study products in Part B of this study, the Zika vaccine and the salt water solution (or placebo). Half of the people in the study will get the vaccine and half will get the placebo.

1. Vaccine: In this study, the vaccine being tested is VRC-ZKADNA090-00-VP which is called the 'Zika DNA vaccine' or 'Zika vaccine'. The Zika vaccine was developed by the Vaccine Research Center (VRC) at the US NIH. It was made at the VRC Pilot Plant in Frederick, Maryland, US.

Vaccines are given to help the body fight off an infection. When you get a dose of this vaccine, it should cause your body to make a small amount of Zika protein. Your body may use this protein to build an immune response against Zika.

There is no Zika virus in this vaccine. You cannot get Zika infection from this vaccine.

You should not expect this experimental Zika vaccine to protect you from Zika infection. You must take steps to protect yourself if you think you might be exposed to Zika in your environment. You should avoid mosquitos, use mosquito repellant, wear long sleeves and pants, and use bed nets at night. If you have any side effects that seem like Zika infection (including fever, rash, eye pain, red eyes, muscle aches, headache, or joint pain) while on the study, tell the study team right away so we can check you as soon as possible.

2. Placebo: The placebo in this study is a sterile salt water solution made for injection into people. It has no vaccine in it. We use the placebo as a control for the vaccine, so we can compare to the vaccine and see how it works.

ELIGIBILITY

You may qualify to take part in this study if:

- you are between [**insert site-specific age range that applies to minors]** years of age,
- you agree not to become pregnant for at least 12 weeks after you get the last product administration, which is about 5 months after the study begins,
- you have physical exam and blood test results that meet study requirements, and
- you do not have any serious medical problems as determined by your screening.

STUDY PROCEDURES

About 2400 people will take part in Part B of this study. If you agree to join Part B, you will be assigned to one of the two study groups by chance (like flipping a coin). You and the clinic staff will not know which study product you are getting until after the study is over.

You will get a total of 3 product administrations. A product administration will be given at 3 separate visits that are each about 4 weeks apart. You will get 2 injections at each product administration visit. We will give all injections using the needle-free injection device called the PharmaJet Stratis® Needle Free Jet Injector (PharmaJet). PharmaJet injections will be given into the upper muscle on each arm. In special cases, PharmaJet injections may also be given into the muscle on the upper thigh.

PharmaJet injects the vaccine into your body without using a needle. Instead of a needle, PharmaJet uses high pressure to push the vaccine through your skin into the muscle. Even though there is no needle, it may still cause pain. Needle-free devices have been used to give vaccines and other medications since the 1940s. This device has been cleared by the FDA for giving vaccine injections into the muscle. Studies have shown that some people who get injections with PharmaJet have more local reactions at the injection site than people who get injections with needle and syringe. However, the local reactions were mild.

If you are a female who is able to get pregnant, you will be given a pregnancy test before you get each product administration. The test must show that you are not pregnant before we can give you the study product.

We will watch you for at least 15 minutes after you get each full dose of study product, which is after you get both injections.

We will ask you to complete a diary card for 7 days after each product administration. You will use the diary card to write down your highest temperature each day and any side effects that you feel. You will also need to look at the injection sites each day and write down how it looks and any side effects that you see. We will give you a thermometer and a measuring device to do this. We will ask you to review your diary card with us about a week later.

The clinic staff is available to you by phone 24 hours a day to report any unexpected side effects. If you have any concerning side effects or if you feel sick, you should tell the clinic right away. We may ask you to come into the clinic for an examination before your next scheduled visit. It is very important that you follow the instructions we give you.

Follow-Up Visits

You will be in the study for about 2 years after you get the first product administration. You will have about 19 to 25 clinic visits and 3 telephone contacts. Each clinic visit will last about [**insert site standard length of clinic visit**].

At each visit, we will ask you about any health changes or problems. We will ask how you are feeling and if you have taken any medications. At scheduled study visits, we will draw about 1-13 tubes of blood from you, depending on the visit. If any of your test results show a health problem, we will tell you about it as soon as possible. You might need to have extra clinic visits and laboratory tests if you have health changes that we need to check.

Experimental vaccine studies like this one follow a set schedule. The study schedule for your visits allows some flexibility, but it is important that you work with the staff to follow the set schedule as much as possible. You should try to not miss any visits.

Sample Collection for Zika Diagnosis

At any time during the study, if you think you have Zika infection, you must contact our clinic right away. We will ask you to come in for a clinical examination and we may collect blood and urine so that we can test you for Zika infection. If you have a rash or another sign or symptom of illness that could possibly be a Zika infection, we may take a photograph of the affected area with your permission. These photographs will not identify you in any way and will only be used by the study team to evaluate your illness. We may also test for other infections that have symptoms similar to Zika infection.

We will tell you the results of your test for Zika infection but it may take several weeks to get the results. It is very important that you get tested for Zika infection at our clinic **only** and that you do not get tested elsewhere unless it is necessary for your health, for example, while traveling.

Sample Collection for Zika Research

Many people who have Zika infection do not feel sick even when there is virus in their blood, urine, or other bodily fluids. As part of this study, we will collect blood samples from you about once a month for the first year and then every two months for the whole study (which is 96

weeks) so we can test for Zika infection. The sample collection plans may change if you get Zika infection. We will collect these samples for research purposes only.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time during the study. There is no penalty or loss of benefits for choosing to leave the study at any time.

MONITORING OF THE STUDY

This study will be monitored by a group of physicians and scientists associated with the US NIH. This group will review the study information and will pay close attention to any reactions that people have to the study products.

STORED SAMPLES

We will collect blood and other bodily fluids such as urine from you during this study. We will keep these samples to study your immune response to the study product and for future research to learn more about Zika, vaccines, the immune system or other related medical conditions. The urgency of the Zika epidemic has accelerated the development of Zika tests and assays. Samples from study subjects may be an important part in the development of new assays to diagnose and to study Zika infections. No genetic research (deoxyribonucleic acid [DNA] testing) will be done on these samples.

[**Add as required per local/national regulations**]: Research samples will be shipped to the Fisher BioServices (Germantown, MD, US) storage facility. Research samples may be stored for up to 20 years. Stored samples may be sent for testing by any of the following laboratories:

- VRC/NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL; Rockville, MD, US)
- NIAID Laboratory of Infectious Diseases (LID; Bethesda, MD, US)
- Battelle, Biomedical Research Center (West Jefferson, OH, US)
- Z-Quick/University of Miami Life Science and Technology Park (Miami, FL, US)
- Blood Systems Research Institute (BSRI, San Francisco, CA, US)
- PaxVax (San Diego, CA, US)

As new tests are developed, additional laboratories may use your stored samples for testing. These laboratories are unknown at this time.

Results from the research done with your stored samples are not for diagnostic purposes or medical care. Therefore, the results will not be part of your medical record.

Labeling of Stored Samples: Your stored samples will be labeled by a special code or number that only the study team can link to you. Any identifying information about you, like your name or date of birth, will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

Future Studies: In the future, other researchers at NIH or outside of NIH may wish to study your stored samples. When the study team shares your samples, they will be marked with a code. Your samples will not have any information on them that could identify you. Some information about you, such as your gender, age, health history, or ethnicity may be shared. Any

future research done with your samples will be done in a way that protects the rights and privacy of study subjects.

Your stored samples will be used only for research and will not be sold. The research done with your samples may be used to develop new products in the future but you will not get payment for these products.

HUMAN DATA SHARING

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

You may stop participating in this study at any time and withdraw permission for your individual data, specimens, and health information to be used for additional or future research. You may ask to have your research data destroyed. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

POSSIBLE STUDY RISKS

Possible **risks from the injections:** Temporary stinging, pain, redness, soreness, itchiness, swelling, or bruising. Injections given with the needle-free device have been shown to cause a small cut at the injection site. A small scab may form within 1 to 2 weeks after the injection is given. There is a very small chance of infection.

There is also a small chance that the needle-free device could not work properly. This includes the syringe breaking and study product spraying during administration. No subjects were harmed when the device did not work. As a result, we ask that you wear safety glasses while we give the injections.

Possible **risks of blood drawing:** Pain, bleeding, bruising, feeling lightheaded, or fainting, and rarely, infection at the site where blood is taken.

Possible **risks from any vaccine:** Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired or unwell. Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after an injection and typically last 1 to 3 days. Medicines, such as acetaminophen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction with symptoms such as hives, trouble breathing, or sudden weakness may happen shortly after any vaccination. This is called “anaphylaxis” and may be life-threatening. While you are waiting in the clinic after the injections, we will monitor you for anaphylaxis. Treatment for anaphylaxis will be given right away if it happens.

Possible **risks of DNA vaccines:** Temporary drop in white blood cell count, sore arm, skin rash or hives, some people get a small red bump and then a scab for a few days where the injection is

given. The NIH has tested many similar vaccines made by the VRC and these vaccines were found to be safe and well-tolerated. We expect this vaccine to be like the ones tested before.

***Possible* risks of the Zika DNA vaccine:** As of July 2018, this Zika vaccine has been tested in 45 subjects in the Phase 1 study, VRC 320. The most common complaints after injection by PharmaJet are mild headache, feeling tired or unwell, and mild pain and bruising at the injection site.

A very similar Zika vaccine has been tested in 80 subjects in the Phase 1 study, VRC 319. As of July 2018, that experimental vaccine was found to be safe for additional studies in humans. The most common complaints after injection by needle and syringe have been arm soreness, headache, muscle aches and feeling tired or unwell.

This Zika vaccine does not contain Zika virus. Guillain-Barré syndrome has not been seen with similar vaccines or vaccines made against similar viruses. We do not know if there is a risk of Guillain-Barré syndrome from the study vaccine. However, we have to be very cautious and observant with a Zika vaccine. This is because natural Zika infection seems to be associated with Guillain-Barré syndrome and we don't know how Zika might cause Guillain-Barré syndrome. You should tell the study team if you develop weakness or tingling in your arms or legs or any other unusual symptoms.

***Possible* risks during Pregnancy:** We do not know if getting the study products will affect a fetus. Therefore, women and adolescents who can get pregnant must agree to use an effective method of birth control starting at least 21 days before getting the first product administration until 12 weeks after the last product administration. We will discuss effective birth control methods with you. If you are pregnant or want to become pregnant in the next 20 weeks, you cannot participate.

During the study, if you think you might be pregnant, you must tell the clinic staff right away. If you are pregnant, you will not get any more study product. We will give you resources you can use to learn about protecting yourself from getting Zika infection. You will be asked to continue with some follow-up visits. We will ask you about the outcome of the pregnancy.

Unknown risks: We do not know if the study product will affect how you respond to any future Zika infection or Zika vaccine that you may get in the future. There may be side effects from the study products, even serious or life threatening ones, that we do not yet know about. We will tell you if we learn about any important new findings or serious side effects of the vaccine during the study that may change your mind about your willingness to continue participation.

You may not donate blood while taking part in this study. You may not donate blood for one year after the date of your last product administration.

POSSIBLE BENEFITS

This study is not designed to benefit you or to protect you from Zika infection. You and others may benefit in the future from the information that we learn from the study.

COSTS OF PARTICIPATION

There are no costs to you for taking part in this study. You or your health insurance will have to pay for all medical costs for medical care that you get outside of this study. It is possible that you may have some costs that are not covered by the study compensation we give you.

COMPENSATION TO YOU FOR TAKING PART IN THE STUDY

You will be compensated [**insert site /EC-approved amount**] for taking part in this study as follows: [**insert site plan**]. Total compensation will be based on the number of study visits you attend and the number of product administrations you get [or **insert site plan**].

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT

The study doctor can take you out of this study without your consent if*:*

- continuing in the study could hurt you,
- you do not follow study instructions or keep your appointments, or
- the study is stopped by the US NIH, FDA, or regulatory authorities.

If you agree to take part in this study, it is important for you to keep all of your appointments. However, if you do not want to stay in the study, you can leave at any time. You will not lose any benefits that you would have had if you had not joined the study.

If you get at least one product administration, we will ask you to continue with your planned follow-up visits until the end of the study. It is important that we continue to check your health even if you do not get the second or third product administrations.

ALTERNATIVES

This study is not designed to treat or prevent any disease. You may choose not to take part.

CONFIDENTIALITY

[**Site/country-specific information on confidentiality may be added to this section**.]

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

Results of US NIH-supported research studies may also be reported in medical journals, on the internet or at scientific meetings. These reports will not have information that can identify you.

In most cases, the US NIH will not release any information about your research participation without your written permission. However, if you sign a release of information form, for example, for an insurance company, the insurance company gets information from your medical record. This information might affect (either positively or negatively) if the insurance company sells insurance to you.

POLICY REGARDING RESEARCH-RELATED INJURIES

The study site will provide immediate medical care for any injury resulting from you being in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the US NIH or the US Federal Government. However, you have the right to seek legal action if you think that your injury has a good reason for such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research subject, or about any research-related injury, call the Principal Investigator [**insert site PI information**]. You may also call the Study Coordinator [**insert site SC information**] or the Patient Representative at [**insert site Patient Representative, as applicable**].

Please keep a copy of this form in case you want to read it again.

SUBJECT ASSENT

I have had this study explained to me in a way that I understand, and I have had the chance to ask questions. All my questions have been answered to my satisfaction. I agree to take part in this study.

Subject Name (print):	Date and Time:
Signature:	

PARENT/GUARDIAN CONSENT

I/we have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. All my/our questions have been answered to my/our satisfaction. I/we hereby give permission for my/our child to take part in this study.

Parent/Guardian (1) *permission for minor patient, if applicable* (print):	Date:
Signature:	
Parent/Guardian (2, if applicable per site/country regulations) *permission for minor patient, if applicable* (print):	Date:
Signature:	

Investigator Name (print):	Date:
Signature:	

APPENDIX II: PROTOCOL TEAM AND CONTACT INFORMATION

APPENDIX III: SCHEDULE OF EVALUATIONS

TABLE A: SCHEDULE OF EVALUATIONS – SCREENING (PART A and PART B)		
Visit Number		01
Week of Study		Week -8 to Day 0
[1]Day of Study		Day -56 to Day 0
Screening	**[4]Tube**	**Screen**
Assessment of Understanding (AoU)		X
Informed Consent		X
Enrollment		X
Pregnancy Prevention Counseling		X
HIV Prevention Counseling		X
Screening Laboratory Tests		
Pregnancy Test (urine or serum)		[2]X
CBC with differential	EDTA	3
ALT, Creatinine	SST	4
HIV Test	SST	4
Clinical Evaluations		
Medical History		X
[3]Physical Examination		X
[4]Research Samples		
Serum for storage	SST	32
PBMC and plasma for storage	EDTA	[5][20]
Total Blood Volume (mL)		**63**

[1] Screening evaluations may be repeated or completed over more than one visit, if needed. Screening research blood draw and consent obtained more than 56 days prior to enrollment are not required to be repeated.
[2] A pregnancy test is not required for women determined to be of non-childbearing potential or for men.
[3] Physical examination assesses eligibility criteria and includes measurement of vital signs and height/weight.
[4] Tube types/volumes are shown to estimate blood volumes in mL. Different tubes for clinical evaluations may be used to meet site requirements but research sample tubes must be used as shown or as instructed by the IND Sponsor.
[5] Brackets [ ] indicate that only approved sites will collect the samples for PBMC and plasma storage.

TABLE B: SCHEDULE OF EVALUATIONS – PART A															
Visit Number		02	02A	03	03A	03B	04	04A	04B	05	06	07	08	09	10
Week of Study		W0	W1	W4	W5	W6	W8	W9	W10	W12	W16	W20	W24	W28	W32
Day of Study		D0	D7	D28	D35	D42	D56	D63	D70	D84	D112	D140	D168	D196	D224
Clinical Evaluations	[4]**Tube**														
Medical History Review		X		X		X	X		X	X	X	X	X	X	X
Vital Signs		X		X		X	X		X	X	X				
[1]Targeted Physical Examination		[X]		[X]		[X]	[X]		[X]	[X]	[X]	[X]	[X]	[X]	[X]
[2]Pregnancy Prevention Counseling		X		X		[X]	X		[X]	[X]	X	X	[X]	[X]	[X]
[2]Pregnancy Test		[X]		X		[X]	X		[X]	[X]	X	X	[X]	[X]	[X]
Eligibility Confirmation		X													
Randomization		X													
Product Administration		X		X			X								
Begin Diary Card		X		X			X								
Phone Contact (clinic visit if needed)			X		X			X							
CBC with differential	EDTA	3		3		3	3		3	3	3				
ALT	SST	4		4		4	4		4	4	4				
Research Samples															
Serum	SST	40		16		16	16		16	16	16	16	16	16	16
[3]PBMC and plasma	EDTA	[40]		[40]		[40]	[40]		[40]	[40]	[40]	[40]	[40]	[40]	[40]
Daily Volume (mL)		**87**	**-**	**63**	**-**	**63**	**63**	**-**	**63**	**63**	**63**	**56**	**56**	**56**	**56**
Cumulative Volume (mL)		**87**	**87**	**150**	**150**	**213**	**276**	**276**	**339**	**402**	**465**	**521**	**577**	**633**	**689**

Visit windows: Visits 02A, 03A, 04A (+3 days); Visits 03B and 04B (±2 days); Visits 03, 05, 06, 07, 08, 09, 10 (±7 days); Visit 04 (-7 days/+14 days; product administrations must be at least 21 days apart). Schedule Visit 02A relative to Visit 02, Visit 03A and 03B relative to Visit 03, Visits 04A through 10 relative to Visit 04, if all product administrations are given as scheduled. Refer to Section 4.2.6.1 for scheduling instructions if all product administrations are not given as scheduled.

[1] Targeted physical examination is only performed as needed, based on subject report or other indications of illness; brackets [ ] indicate optional, as needed.

[2] Pregnancy prevention counseling and pregnancy testing are to be added to every visit, as shown in brackets [ ], for any subject of childbearing potential with confirmed ZIKV infection. A pregnancy test and pregnancy prevention counseling are not required for women determined to be of non-reproductive potential or for men throughout the study.

[3] Brackets [ ] indicate that only approved sites will collect samples for PBMC and plasma storage. Tube types/volumes are shown to estimate blood volumes in mL.

[4] Different tubes for clinical evaluations may be used to meet site requirements but research sample tubes must be used as shown or as instructed by the IND Sponsor.

TABLE C: SCHEDULE OF EVALUATIONS – PART B															
Visit Number		02	02A	03	03A	04	04A	05	06	07	08	09	10	11	12
Week of Study		W0	W1	W4	W5	W8	W9	W12	W16	W20	W24	W28	W32	W36	W40
Day of Study		D0	D7	D28	D35	D56	D63	D84	D112	D140	D168	D196	D224	D252	D280
Clinical Evaluations	[6]**Tube**														
[1]Medical History Review		X		X		X		X	X	X	X	X	X	X	X
Vital Signs		X		X		X			X						
[2]Targeted Physical Examination		[X]		[X]		[X]		[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
[3]Pregnancy Prevention Counseling		X		X		X		[X]	[X]	X	[X]	[X]	[X]	[X]	[X]
[3]Pregnancy Test		X		X		X		[X]	[X]	X	[X]	[X]	[X]	[X]	[X]
Eligibility Confirmation		X													
Randomization		X													
Product Administration		X		X		X									
Begin Diary Card		X		X		X									
Phone Contact (clinic visit if needed)			X		X		X								
CBC with differential	EDTA	3		3		3			3						
ALT	SST	4		4		4			4						
Research Samples															
Serum	SST	32		16		16		16	16	8	8	8	8	8	8
[4]PBMC and plasma	EDTA	[40]		[40]		[40]		[40]	[40]						
[5]Whole blood (red blood cells and plasma)	EDTA	10		10		10		10	10	10	10	10	10	10	10
Daily Volume (mL)		**89**	**-**	**73**	**-**	**73**	**-**	**66**	**73**	**18**	**18**	**18**	**18**	**18**	**18**
Cumulative Volume (mL)		**89**	**89**	**162**	**162**	**235**	**235**	**301**	**374**	**392**	**410**	**428**	**446**	**464**	**482**

Visit windows: Visits 02A, 03A, 04A (+3 days); Visits 03, 05, 06, 07, 08, 09, 10, 11, 12 (±7 days); Visit 04 (-7 days/+14 days; product administrations must be at least 21 days apart). Schedule Visit 02A relative to Visit 02, Visit 03A relative to Visit 03, Visits 04A through 26 relative to Visit 04, if all product administrations are given as scheduled. Refer to Section 4.2.6.1 for scheduling instructions if all product administrations are not given as scheduled.

[1] Full medical history review at screening, then perform an interim medical history review from V02 through end of study.

[2] Targeted physical examination is only performed as needed, based on subject report or other indications of illness; brackets [ ] indicate optional, as needed.

[3] A pregnancy test and pregnancy prevention counseling are not required for females of non-childbearing potential or for men throughout the study. Pregnancy prevention counseling and pregnancy testing are to be added to every visit, as shown in brackets [ ], for any subject of childbearing potential with ZIKV infection.

[4] Brackets [ ] indicate that only approved sites will collect samples for PBMC and plasma.

[5] Scheduled collection of whole blood and serum research samples to evaluate asymptomatic ZIKV infection can occur outside of visit windows without permission but should be recorded as a protocol deviation. Every effort should be made to obtain these samples once a month.

[6] Tube types/volumes are shown to estimate blood volumes in mL. Different tubes for clinical evaluations may be used to meet site requirements but research sample tubes must be used as shown or as instructed by the IND Sponsor.

TABLE C: SCHEDULE OF EVALUATIONS – PART B (continued)									
Visit Number		13	14	16	18	20	22	24	26
Week of Study		W44	W48	W56	W64	W72	W80	W88	W96
Day of Study		D308	D336	D392	D448	D504	D560	D616	D672
Clinical Evaluations	[6]**Tube**								
[1]Medical History Review		X	X	X	X	X	X	X	X
[2]Targeted Physical Examination		[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
[3]Pregnancy Prevention Counseling		[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
[3]Pregnancy Test		[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
CBC with differential	EDTA	3							
ALT	SST	4							
Research Samples									
Serum	SST	16	8	8	8	16	8	8	16
[4]PBMC and plasma	EDTA	[40]				[40]			[40]
[5]Whole blood (red blood cells and plasma)	EDTA	10	10	10	10	10	10	10	10
Daily Volume (mL)		**73**	**18**	**18**	**18**	**66**	**18**	**18**	**66**
Cumulative Volume (mL)		**555**	**573**	**591**	**609**	**675**	**693**	**711**	**777**

Visit windows: Visits 13 through 26 (±7 days).

[1] Perform an interim medical history review from V02 through end of study.

[2] Targeted physical examination is only performed as needed, based on subject report or other indications of illness; brackets [ ] indicate optional, as needed.

[3] A pregnancy test is not required for females of non-childbearing potential or men throughout the study. Pregnancy prevention counseling and pregnancy testing are to be added to every visit, as shown in brackets [ ], for any subject of childbearing potential with ZIKV infection.

[4] Brackets [ ] indicate that only approved sites will collect samples for PBMC and plasma storage.

[5] Scheduled collection of research blood samples to evaluate asymptomatic ZIKV infection can occur outside of visit windows without permission but should be recorded as a protocol deviation. Every effort should be made to obtain these samples once a month.

[6] Tube types/volumes are shown to estimate blood volumes. Different tubes for clinical evaluations may be used to meet site requirements but research sample tubes must be used as shown or as instructed by the IND Sponsor.

* As of protocol version 5.0 approval at site, study visits 15, 17, 19, 21, 23, and 25 are not required. If the visit is scheduled to occur for the subject prior to V5.0 approval, then the visit should be conducted.

APPENDIX IV: ASSESSMENT OF RELATIONSHIP TO STUDY PRODUCT AND ADVERSE EVENT SEVERITY GRADING

Assessment of Causality Relationship of an Adverse Event to Study Product:

The relationship between an adverse event (AE) and the product will be assessed by the investigator on the basis of his or her clinical judgment and the definitions below.

- **Definitely Related**. The AE and study product are related in time and a direct association can be demonstrated.
- **Probably Related**. The AE and study product are reasonably related in time and the AE is more likely explained by study product than other causes.
- **Possibly Related**. The AE and study product are reasonably related in time but the AE can be explained equally well by causes other than study product.
- **Not Related**. There is not a reasonable possibility that the AE is related to the study product.

For purposes of preparing data reports in which AE attributions are limited to "**Related**" or "**Not Related**"; in this protocol, the "Definitely, Probably and Possibly" attributions will be mapped to the "Related" category. The definitions that apply when these two categories alone are used are as follows:

- **Related** – There is a reasonable possibility that the AE may be related to the study product.
- **Not Related** – There is not a reasonable possibility that the AE is related to the study product.

Grading the Severity of Adverse Events:

The FDA Guidance for Industry (September 2007): "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers [Subjects] Enrolled in Preventive Vaccine Clinical Trials" is the basis for the severity grading of AEs in this protocol. Several modifications were made to the table as follows:

- "Emergency room visit" is not automatically considered a potentially life-threatening event; these words have been removed from any "grade 4' definition where they appear in the table copied from the guidance document.
- Any laboratory value shown as a "graded" value in the table that is within the institutional normal range will not be severity graded or recorded as an AE.
- Severity grading for hemoglobin decrease on the basis of the magnitude of decrease from baseline is not applicable at the grade 1 level; only absolute hemoglobin will be used to define grade 1 decrease. Increases in hemoglobin are AEs only for values above the upper limit of normal and are graded by the systemic illness clinical criteria.
- Severity grading definition for Grade 4 local reaction to injectable product (Erythema/Redness and Induration/Swelling) included added text "requiring medical attention".
- 1 X ULN was removed from the definition for PT increase.

When not otherwise specified in the table, the following guidance will be used to assign a severity grade:

Grade 1 (Mild): No effect on activities of daily living

Grade 2 (Moderate): Some interference with activity not requiring medical intervention

Grade 3 (Severe): Prevents daily activity and requires medical intervention

Grade 4 (Potentially Life-threatening): Hospitalization; immediate medical intervention or therapy required to prevent death.

Grade 5 (Death): Death is assigned a Grade 5 severity.

Only the single AE that is assessed as the primary cause of death should be assigned "Grade 5" severity.

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers [Subjects] Enrolled in Preventive Vaccine Clinical Trials
FDA Guidance - September 2007

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospitalization
[1]Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis requiring medical attention
[2] 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 requiring medical attention

[3] Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
[4] Fever (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia
[5] Bradycardia - beats per Minute	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

1. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
2. Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
3. Subject should be at rest for all vital sign measurements.
4. Oral temperature; no recent hot or cold beverages or smoking.
5. When resting heart rate is between 60 – 100 beats per minute, use clinical judgment when characterizing Bradycardia among some healthy subject populations, for example, conditioned athletes.

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

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

B. Tables for Laboratory Abnormalities

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

Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150

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

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
*** "ULN" is the upper limit of the normal range.

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) decrease from baseline value - gm/dL	not applicable	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) decrease from baseline value – gm/dL	not applicable	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.10 – 1.20 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

Purpose

This is a research study of an experimental vaccine against Zika virus infection. "Experimental" means that the study vaccine has not been approved by the US Food and Drug Administration (FDA). The FDA allows this vaccine to be used for research purposes only. This vaccine has been given to people in a Phase 1 study but we do not know if the vaccine works.

The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study immune responses to the vaccine including cells that may recognize and fight Zika virus. This study will take place in areas where Zika outbreaks are happening or may happen.

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine.

A total of 90 subjects at up to 2 institutions will be asked to participate in this part of the study.

You will be one of approximately 45 subjects to be asked to participate at Baylor College of Medicine.

The research will be conducted at the Baylor College of Medicine Vaccine Research Center.

SCREENING

Before you can take part in this experimental Zika DNA vaccine study, your health will be checked so we can decide if you qualify. You will need to sign this consent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health. These blood tests include a complete blood count, a kidney and liver function test. We will also ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy. We will review the test results with you and tell you if the results show that you are eligible to join the study.

You will also be tested for Human Immunodeficiency Virus (HIV). If your HIV test is positive you will not be able to be in this study. We will help refer you to a doctor (either a primary care physician or an infectious diseases specialist). If your HIV test result is positive it will need to be reported to the local health department per the local requirements. We will discuss the risks related to getting HIV and how to reduce the risk of getting HIV with you.

During screening, we will also collect some blood to store for research.

STUDY PLAN

This study has 3 groups, you will be in one of the 3 groups.

You will either get vaccine at doses of 4 milligrams (mg) or 8 mg split and you will either get 2 or 4 injections.

If you qualify for the study and participate you will be in the study for 32 weeks or about 8 months.

Please see the table provided by the study team that outlines the 3 groups for this study.

STUDY PRODUCT (The VACCINE YOU WILL GET)

The study product (vaccine) being tested in this study is VRC-ZKADNA090-00-VP, which is called the 'Zika DNA vaccine' or 'Zika vaccine'. The Zika vaccine was developed by the Vaccine Research Center (VRC) at the US NIH. It was made at the VRC Pilot Plant in Frederick, Maryland, US.

Vaccines are given to help the body fight off an infection. When you get a dose of this vaccine, it should cause your body to make a small amount of Zika protein. Your body may use this protein to build an immune response against Zika. We do not know if the vaccine works.

There is no Zika virus in this vaccine. You cannot get Zika infection from this vaccine.

You should not expect this experimental Zika vaccine to protect you from Zika infection. If you live in or travel to an area with Zika virus you must take steps to protect yourself if you think you might be exposed to Zika in your environment. Ways to reduce the risk are to avoid mosquitos, use mosquito repellant, wear long sleeves and pants, and use bed nets at night. If you have any side effects that seem like Zika infection (including fever, rash, eye pain, red eyes, muscle aches, headache, or joint pain) while on the study, tell the study team right away so we can check you as soon as possible.

ELIGIBILITY

You may qualify to take part in this study if:

1. You are between 18 and 35 years of age,
2. You agree not to become pregnant for at least 12 weeks after you get the last injection (vaccination), which is about 5 months after the study begins
3. You have physical exam and blood test results that meet study requirements
4. You do not have any serious medical problems as determined by your screening

You cannot be in this study if you have any of the following: a history of confirmed Zika infection, a serious reaction to vaccines, chronic angioedema (swelling of face) or chronic urticara (hives), asthma that is not well controlled, diabetes, a disease that affects your immune system, uncontrolled high blood pressure, a bleeding disorder, active cancer, seizure or treatment for a seizure disorder in the last 3

years, or if you have had your spleen removed. There may be other medical conditions that you have that will disqualify you from being in the study. You may also not be eligible for this study if you are taking certain medications including medications that may affect your immune system (like chronic steroids, chemotherapy or disease-modifying antibodies). After signing this consent form the study doctor will review your health with you.

You cannot be in this study if you are in another study that is also giving you an experimental drug or product.

You may also not be eligible for this study if you are a not able to come to the clinic for follow up visits . The study team will review the schedule with you. If you have any questions please ask the study team.

STUDY PROCEDURES

About 90 people will take part in Part A of this study. If you are eligible for the study and agree to join Part A, you will be assigned to one of the three study groups by chance (like flipping a coin). Once you are on the study, you will know which group you are in.

You will get the study vaccine 3 times at 3 separate visits that are each about 4 weeks apart. Depending on which study group you are in, you will get either 2 or 4 injections at each vaccination visit. We will give all injections using the needle-free injection device called the PharmaJet Stratis® Needle Free Jet Injector (PharmaJet). In all study groups, PharmaJet injections will be given into the deltoid muscle, a muscle in the upper part of your arms. In some study groups, PharmaJet injections will also be given into the muscle on the upper thigh.

PharmaJet injects the vaccine into your body without using a needle. Instead of a needle, PharmaJet uses high pressure to push the vaccine through your skin into the muscle. Even though there is no needle, it may still cause pain. Needle-free devices have been used to give vaccines and other medications since the 1940s. This device has been cleared by the FDA for giving vaccine injections into the muscle. Studies have shown that some people who get injections with PharmaJet have more local reactions at the injection site than people who get injections with needle and syringe. However, the local reactions were mild.

You will be in the study for about 8 months after you get the first vaccination. You will have about 11 clinic visits and 3 telephone contacts scheduled. The vaccine visits may last 2 to 2.5 hours. The follow up clinic visit will last about 30 minutes.

In summary your visit schedule will be:

Visit 1 - Screening Visit

Visit 2 (Day 0) - First Vaccination Visit
Visit 2A (Day 7) - Phone call
Visit 3 (Day 28) - Second Vaccination Visit
Visit 3A (Day 35) - Phone call
Visit 3B (Day 42) - Clinic Follow-up with blood draw
Visit 4 (Day 56) - Third Vaccination Visit
Visit 4A (Day 63) - Phone call
Visit 4B (Day 70) - Clinic Follow-up with blood draw
Visit 5 (Day 84) - Clinic Follow-up with blood draw
Visit 6 (Day 112) - Clinic Follow-up with blood draw
Visit 7(Day 140) - Clinic Follow-up with blood draw
Visit 8 (Day 168) - Clinic Follow-up with blood draw
Visit 9 (Day 196) - Clinic Follow-up with blood draw
Visit 10 (Day 224) - Clinic Follow-up with blood draw

At each visit, we will ask you about any health changes or problems. We will ask how you are feeling and if you have taken any medications. At scheduled clinic study visits, we will draw about 4 to 11 tubes of blood from you, depending on the visit. If any of your test results show a health problem, we will tell you about it as soon as possible. You might need to have extra clinic visits and laboratory tests if you have health changes that we need to check.

On Vaccination Visits (Visits 2, 3, and 4)

If you are a female who is ableto get pregnant, you will be given a pregnancy test before you get the vaccine on each day. The test must show that you are not pregnant before we can give you the vaccine.

We will watch you for at least 15 minutes after you get each full dose of the vaccine, which is after you get all 2 or 4 injections.

We will ask you to complete a diary card for 7 days after each vaccination. You will use the diary card to write down your highest temperature each day and any side effects that you feel. You will also need to look at the injection sites each day and write down how they look and any side effects that you see. We will give you a thermometer and a measuring device to do this. We will ask you to review your diary card with us about a week later.

The study staff is available to you by phone 24 hours a day to report any unexpected side effects. If you have any concerning side effects or if you feel sick, you should tell the clinic right away. We may ask you to come into the clinic for an examination before your next scheduled visit. It is very important that you follow the instructions we give you.

During screening we will collect up to 15 mL or 1 tablespoon of blood to check your complete blood counts (CBC) and perform a liver function test (ALT or alanine aminotransferase) and a kidney function

test (Cr or creatinine).

On visits 2, 3, 3B, 4, 4B, 5 and 6 we will be collecting about half a tablespoon (about 7 mL) of blood to check your CBC and ALT. We will review the results with you before or at your next visit.

On visits 1, 2, 3, 3B, 4, 4B, 5, 6, 7, 8, 9, 10 we will also be collecting about 4-5 tablespoons (about 56-80 mL) of blood your immune responses (your body's way of protecting itself). These tests are for the research.

A total of about 51 tablespoons or 750 mL of blood will be collected during the study over about 32 weeks.

Experimental vaccine studies like this one follow a set schedule. The study schedule for your visits allows some flexibility, but it is important that you work with the staff to follow the set schedule as much as possible. You should try to not miss any visits. The study team will provide you with a study schedule and will review the schedule and procedures at each clinic visit with you.

If you agree to take part in this study, it is important for you to keep all of your appointments.

If you get at least one vaccination, we will ask you to continue with your planned follow-up visits to monitor your health until the end of the study. It is important that we continue to check your health even if you do not get the second or third vaccinations.

Sample Collection for Zika Diagnosis

At any time during the study, if you think you have Zika infection, you must contact our clinic right away. We will ask you to come in for a clinical examination and we may collect blood, urine and other bodily fluid samples, such as saliva, so that we can test you for Zika infection. We may also test for other infections that have symptoms similar to Zika infection.

We will tell you the results of your test for Zika infection but it may take several weeks to get the results. It is very important that you get tested for Zika infection at our clinic and that you do not get tested elsewhere unless it is necessary for your health, for example, while traveling.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time during the study. There is no penalty or loss of benefits for choosing to leave the study at any time.

MONITORING OF THE STUDY

This study will be monitored by a group of physicians and scientists associated with the US NIH. This group will review the study information and will pay close attention to any reactions that people have to the study product (vaccine).

STORED SAMPLES

We will collect blood and other bodily fluids such as urine (if testingfor Zika infection testing) during this study. We will keep these samples to study your immune response to the study product and for future research to learn more about Zika, vaccines, the immune system or other medical conditions. Results from the research done with your stored samples are not for medical care and will not be in your medical record.

Labeling of Stored Samples: Your stored samples will be labeled by a special code or number that only the study team can link to you. Any identifying information about you, like your name or date of birth, will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

Future Studies: In the future, other researchers at NIH or outside of NIH may wish to study your stored samples. When the study team shares your samples, they will be marked with a code. Your samples will not have any information on them that could identify you. Some information about you, such as your gender, age, health history, or ethnicity may be shared. Any future research done with your samples will be done in a way that protects the rights and privacy of study subjects.

Your stored samples will be used only for research and will not be sold. The research done with your samples may be used to develop new products in the future but you will not get payment for these products.

By signing this consent form you agree to allow the samples to be stored for future research.

HUMAN DATA SHARING

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

You may stop participating in this study at any time and withdraw permission for your individual data,

specimens, and health information to be used for additional or future research. Studies related to the current research will still be conducted on the samples collected prior to the you withdrawing from the study. Samples and data already collected prior to you withdrawing will be used as per the study but no further samples will be collected.
However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning alcohol abuse
- Specific information concerning drug abuse
- Specific information concerning sickle cell anemia
- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Full Social Security #

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, and NIH: NATIONAL INSTITUTES OF HEALTH and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine is required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research does not involve treatment. Baylor College of Medicine may not condition (withhold or refuse) treating you on whether you sign this Authorization.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, NIH: NATIONAL INSTITUTES OF HEALTH and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: [redacted]
[redacted]

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts
POSSIBLE STUDY RISKS

Possible risks from the injections: Temporary stinging, pain, redness, soreness, itchiness, swelling, or bruising. Injections given with the needle-free device have been shown to cause a small cut at the injection site. A small scab may form within 1 to 2 weeks after the injection is given. There is a very small chance of infection. There is also a small chance that the needle-free device could not work properly. As of June 7, 2017, there have been 6 out of 246 injections that involved device malfunction in VRC 705 Part A. This includes the syringe breaking and study product spraying during administration.

As a result, we ask that you wear safety glasses while we give the injections.

Possible risks of blood drawing: Pain, bleeding, bruising, feeling lightheaded, or fainting, and rarely, infection at the site where blood is taken.

To reduce the risk of infection, the area where the blood will be drawn and where the study injections will be given will be cleaned using an alcohol pad. Sterile (clean) equipment will be used.

Possible risks from any vaccine: Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired or unwell. Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after an injection and typically last 1 to 3 days. Medicines, such as acetaminophen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction with symptoms such as hives, trouble breathing, or sudden weakness may happen shortly after any vaccination. This is called "anaphylaxis" and may be life-threatening. While you are waiting in the clinic after the injections, we will monitor you for anaphylaxis. Treatment for anaphylaxis will be given right away if it happens.

Possible risks of DNA vaccines: Temporary drop in white blood cell count, sore arm, skin rash or hives, some people get a small red bump and then a scab for a few days where the injection is given. The NIH has tested many similar vaccines made by the VRC and these vaccines were found to be safe and well-tolerated. We expect this vaccine to be like the ones tested before.

Possible risks of the Zika DNA vaccine: As of December 2016, this Zika vaccine has been tested in 5 subjects in the Phase 1 study, VRC 320. So far, the most complaints after injection by PharmaJet are mild headache, feeling tired or unwell, and mild pain and bruising at the injection site.
A very similar Zika vaccine has been tested in 80 subjects in the Phase 1 study, VRC 319. As of December 2016, that experimental vaccine was found to be safe for additional studies in humans. So far, the most common complaints after injection by needle and syringe have been arm soreness, headache, muscle aches and feeling tired or unwell.

This Zika vaccine does not contain Zika virus. Guillain-Barré syndrome has not been seen with similar vaccines or vaccines made against similar viruses. We do not know if there is a risk of Guillain-Barré syndrome from the study vaccine. However, we have to be very cautious and observant with a Zika vaccine. This is because natural Zika infection seems to be associated with Guillain-Barré syndrome and we don't know how Zika might cause Guillain-Barré syndrome. You should tell the study team if you develop weakness or tingling in your arms or any other unusual symptoms.

Possible risks during Pregnancy: We do not know if getting the study product will affect a fetus. Therefore, women and adolescents who can get pregnant must agree to use an effective method of birth control starting at least 21 days before getting the first product administration until 12 weeks after the last product administration. We will discuss effective birth control methods with you. If you are

pregnant or want to become pregnant in the next 20 weeks, you cannot participate.

During the study, if you think you might be pregnant, you must tell the clinic staff right away. If you are pregnant, you will not get any more study product. We will give you resources you can use to learn about protecting yourself from getting Zika infection. You will be asked to continue with some follow-up visits. We will ask you about the outcome of the pregnancy.

You may not donate blood while taking part in this study. You may not donate blood for one year after the date of your last product administration.

Unknown risks: We do not know if the study product will affect how you respond to any future Zika infection or Zika vaccine that you may get in the future.

Confidentiality

You will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see your PHI. All records will be kept in a locked file cabinet or maintained in a locked room in our research areas. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Organizations that may inspect and/or copy research records maintained at our research site for quality assurance and data analysis include groups such as National Institute of Allergy and Infectious Diseases (NIAID) and Food and Drug Administration (FDA).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

Results of US NIH-supported research studies may also be reported in medical journals, on the internet or at scientific meetings. These reports will not have information that can identify you.

In most cases, the US NIH will not release any information about your research participation without your written permission. However, if you sign a release of information form, for example, for an insurance company, the insurance company gets information from your medical record. This information might affect (either positively or negatively) if the insurance company sells insurance to you.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

You will receive no direct benefit from your participation in this study. However, your participation may

help the investigators better understand how we can protect people from Zika infection. We do not know if this vaccine will protect you from ZIKV infection. You and others may benefit in the future from the information that we learn from the study. .

Alternatives

You may choose to not participate in this study.

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city or if you have a serious reaction to your study vaccine) or because the entire study is stopped. The sponsor, investigator, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

The study doctor can take you out of this study without your consent if:

- continuing in the study could hurt you,
- you do not follow study instructions or keep your appointments, or
- the study is stopped by the US NIH, FDA, or regulatory authorities.

Subject Costs and Payments

You will not be asked to pay any costs related to this research.

You will be compensated for your time and effort as part of the research study:

Visit 1 - Screening visit - you will receive a voucher for $50 for completion of the visit
During the screening visit, if you do not qualify for the study based on review of your health prior to the blood draw then you will be compensated $25.

Once you are eligible and enroll in the study you will be compensated as follows:

Visits 2, 3, 4: Vaccination visits (Total $300)
$100 for each completed vaccination visit
If it is decided that you will not receive vaccine at a vaccination visit you will be compensated $50 for that visit.

Visits 2A, 3A, 4A: Scheduled Phone call visits (Total $75)
$25 for each scheduled phone call visit completed

Visits 3B, 4B, 5, 6, 7, 8, 9, and 10 Follow-up Clinic Visits (Total $400)
$50 for each scheduled follow-up clinic visit completed

By the end of the study you will receive a total amount of up to $825 for completing the screening visit and all scheduled clinic and phone call study visits.

You will be compensated $50 for any unscheduled clinic visits that may be necessary to follow-up on your health during the study.

The compensation will be distributed at regular intervals during the conduct of the study either by cash (via voucher) or check.

You will also be provided parking reimbursement for the Texas Medical Center parking garages to cover parking expenses you may have during your study visits or reimbursement up to $12 for use of public transportation to and from our clinic visits.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

Research Related Injury

The study site will provide immediate medical care for any injury resulting from you being in research here.

The study doctor will also provide referrals to appropriate health care facilities. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the study or the US NIH or the US Federal Government. However, by signing this consent form you do not give up any of the legal rights you have as a participant in a research study.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, [redacted], and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: [redacted] or her staff at [redacted] during the day and after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is [redacted]. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

Your decision whether or not to participate will not affect your current or future relations with Baylor College of Medicine (BCM).

CONTACT FOR FUTURE STUDIES

We may want to contact you in the future to ask if you would like to participate in another study. If you agree, we would like to keep your name, date of birth, address, phone number, and e-mail address on file. This information will be kept secured and confidential and will not be shared with other investigators

at this or other institutions.

Please INITIAL your decision about permission for us to contact you in the future for upcoming studies (indicate only ONE option):

_____YES, you may contact me in the future by telephone, e-mail, text messaging, or postal mail to inform me of upcoming studies.

_____NO, you may not contact me in the future regarding upcoming studies.

Agreeing to be in this study does not obligate you to participate in any of our future studies and a separate consent document would be signed for any future study.

FUTURE USE OF YOUR RESEARCH SAMPLE

_____ Please initial here to indicate that you understand that by signing this consent form and participating in this study that you agree that your research samples in this study will be stored for future research as explained in this consent form.

Before you sign this consent form we will ask you to complete a questionnaire with 20 True/False questions (an Assessment of Understanding) which is a tool to help make sure you understand the research that you may agree to be part of. You do not have to get all the questions correct, but if you miss any questions the study staff will review the question and the correct answer with you to make sure you understand the research study.

H-40208- A PHASE 2/2B, RANDOMIZED TRIAL TO EVALUATE THE SAFETY, IMMUNOGENICITY AND EFFICACY OF A ZIKA VIRUS DNA VACCINE IN HEALTHY ADULTS AND ADOLESCENTS (VRC 705 VER 5.0 28AUG2018)

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date

H-40208- A PHASE 2/2B, RANDOMIZED TRIAL TO EVALUATE THE SAFETY, IMMUNOGENICITY AND EFFICACY OF A ZIKA VIRUS DNA VACCINE IN HEALTHY ADULTS AND ADOLESCENTS (VRC 705 VER 5.0 28AUG2018)

Background

PRINT NAME: _____

You are invited to take part in a research study at Baylor College of Medicine.

Please read this information and feel free to ask any questions before you agree to take part in the study.

The study is sponsored by the National Institutes of Health (NIH) in Bethesda, MD, U.S. You can choose if you want to take part in this study or not. There is no penalty or loss of benefits for choosing not to take part in this study. Please ask questions and discuss this study with anyone you want. Take as much time as you need to decide. You will be given a signed copy of this consent form.

BACKGROUND ON ZIKA VIRUS

Zika virus was discovered in 1947. It is named after the Zika Forest in Uganda where it was found. Until recently, Zika infections happened in parts of Africa and Asia. Recent outbreaks have been reported in North, Central and South America, the Caribbean, the Pacific Islands, and Africa.

Zika is passed from human to human by infected mosquitos. Zika can also be passed through sex from a person who has Zika to his or her partners, and from a mother to her child during pregnancy. Zika infection causes symptoms that are usually mild and may include fever, rash, joint pain, and conjunctivitis (red eyes). Many times, there are no symptoms at all, so many people do not know that they have been infected. Symptoms usually last from 2 to 7 days. People usually don¿t get sick enough to go to the hospital, and they very rarely die. A person who has been infected once is not likely to get Zika infection again.

Recently, some cases of microcephaly (abnormally small head and brain) and other birth defects were found in babies that were born to mothers who had a Zika infection. Some people who had Zika infection also had rare cases of a severe muscle weakness called Guillain-Barré syndrome. We do not know why some people who get Zika infection develop Guillain-Barré syndrome. Most people who develop Guillain-Barré syndrome recover over time. If you have ever had this condition, you will not qualify for this study.

There is currently no cure for or vaccine to prevent Zika infection.

We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

Purpose

This is a research study of an experimental vaccine against Zika virus infection.
Experimental means that the study vaccine has not been approved by the US Food and Drug Administration (FDA). The FDA allows this vaccine to be used for research purposes only. This vaccine has been given to people in a Phase 1 study. We do not know if the vaccine works. The main purpose of this study is to see if the experimental vaccine is safe and if there are any side effects. We also want to study immune responses to the vaccine including cells that may recognize and fight Zika virus. This study will take place in areas where Zika outbreaks are happening or may happen.

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine.

You will be one of approximately 10 subjects to be asked to participate at Baylor College of Medicine.

The research will be conducted at the Baylor College of Medicine Vaccine Research Center.

SCREENING

Before you can take part in this experimental Zika DNA vaccine study, your health will be checked so we can decide if you qualify. You will need to sign this consent form before screening. If you qualify, then you may take part in the vaccine study.

Screening includes a physical exam and blood tests to check your health. These blood tests include a complete blood count, a kidney and liver function test. We will also ask you about your health history. If you are a female who is able to have children, you will be asked about the possibility of you becoming pregnant while in the study. You will be tested for pregnancy. We will review the test results with you and tell you if the results show that you are eligible to join the study.

You will also be tested for Human Immunodeficiency Virus (HIV). If your HIV test is positive you will not be able to be in this study. We will help refer you to a doctor (either a primary care physician or an infectious diseases specialist). If your HIV test result is positive it will need to be reported to the local health department per the local requirements. We will discuss the risks related to getting HIV and how to reduce the risk of getting HIV with you.

During screening, we will also collect some blood to store for research.

STUDY PLAN

By signing this form you are willing to participate in Part B of this study.
Part B of the study has 2 groups with a total of about 2400 people. We are testing the vaccine in comparison to the placebo, which is a salt-water solution that has no vaccine in it.

STUDY PRODUCTS (The injections)
You will either get vaccine or the placebo.

1. Vaccine
The study product (vaccine) being tested in this study is VRC-ZKADNA090-00-VP, which is called the ¿Zika DNA vaccine¿ or ¿Zika vaccine¿. A total of 4mg of vaccine split into 2 injections will be given. The Zika vaccine was developed by the Vaccine Research Center (VRC) at the US NIH. It was made at the VRC Pilot Plant in Frederick, Maryland, US. The study vaccine is a recombinant DNA vaccine. This means that the vaccine was created and made in a laboratory using genetic codes from the Zika virus.

Vaccines are given to help the body fight off an infection. When you get a dose of this vaccine, it should cause your body to make a small amount of Zika protein. Your body may use this protein to build an immune response against Zika.

There is no Zika virus in this vaccine. You cannot get Zika infection from this vaccine.

We do not know if the vaccine works. You should not expect this experimental Zika vaccine to protect you from Zika infection. If you live in or travel to an area with Zika virus you must take steps to protect yourself if you think you might be exposed to Zika in your environment. Ways to reduce the risk are to avoid mosquitos, use mosquito repellant, wear long sleeves and pants, and use bed nets at night. If you have any side effects that seem like Zika infection (including fever, rash, eye pain, red eyes, muscle aches, headache, or joint pain) while on the study, tell the study team right away so we can check you as soon as possible.

2. Placebo:
The placebo in this study is a sterile salt water solution made for injection into people. It has no vaccine in it. We use the placebo as a control for the vaccine, so we can compare to the vaccine and see how it works.

ELIGIBILITY

You may qualify to take part in this study if:

1. You are between 18 and 35 years of age,
2. You agree not to become pregnant for at least 12 weeks after you get the last injection (vaccination), which is about 5 months after you get your first study product administration
3. You have physical exam and blood test results that meet study requirements, and
4. You do not have any serious medical problems as determined by your screening

You cannot be in this study if you have any of the following: a history of confirmed Zika infection, a serious reaction to vaccines, chronic angioedema (history of swelling of face, lips, or eyes) or chronic urticara (hives), asthma that is not well controlled, diabetes, a disease that affects your immune system, uncontrolled high blood pressure, a bleeding disorder, active cancer, seizure or treatment for a seizure disorder in the last 3 years, or if your spleen does not work well or you have had your spleen removed. There may be other medical conditions that you have that will disqualify you from being in the study. You may also not be eligible for this study if you are taking certain medications including medications that may affect your immune system (like chronic steroids, chemotherapy or disease-modifying antibodies). After signing this consent form the study doctor will review your health with you.

You cannot be in this study if you are currently in another study that is also giving you an experimental drug or product.

You may also not be eligible for this study if you are not able to come to the clinic for follow up visits. The study team will review the schedule with you. If you have any questions please ask the study team.

If you qualify for the study and participate you will be in the study for 96 weeks or about 24 months.

STUDY PROCEDURES

If you are eligible for the study and agree to join Part B, you will be assigned to one of the two study groups by chance (like flipping a coin). You and the clinic staff will NOT know which study product you are getting until after the study is over.

You will get the study product 3 times at 3 separate visits that are each about 4 weeks apart. You will get 2 injections (one in each arm) at each product administration visit. We will give all injections using the needle-free injection device called the PharmaJet Stratis® Needle Free Jet Injector (PharmaJet). In all study groups, PharmaJet injections will be given into the deltoid muscle, a muscle in the upper part of your arms. In special cases, if the injection cannot be given in the deltoid muscle, Pharmajet injections may also be given into the muscle of the upper thigh.

PharmaJet injects the vaccine into your body without using a needle. Instead of a needle, PharmaJet uses high pressure to push the vaccine through your skin into the muscle. Even though there is no needle, it may still cause pain. Needle-free devices have been used to give vaccines and other medications since the 1940s. This device has been cleared by the FDA for giving vaccine injections into the muscle. Studies have shown that some people who get injections with PharmaJet have more local reactions at the injection site than people who get injections with needle and syringe. However, the local reactions were mild.

You will be in the study for about 2 years after you get the first product administration. You will have about 19 to 25 scheduled clinic visits and 3 scheduled telephone contacts. Three clinic visits (for product administration) will last about 3 hours, and the other clinic visits for follow-up and blood draw will

last less than 1 hour, usually about 30 minutes.

In summary your visit schedule will be:

Visit 1 - Screening Visit
Visit 2 (Day 0) - First Vaccination Visit
Visit 2A (Day 7) - Phone call
Visit 3 (Day 28) - Second Vaccination Visit
Visit 3A (Day 35) - Phone call
Visit 4 (Day 56) - Third Vaccination Visit
Visit 4A (Day 63) - Phone call
Visit 5 (Day 84) - Clinic Follow-up with blood draw
Visit 6 (Day 112) - Clinic Follow-up with blood draw
Visit 7(Day 140) - Clinic Follow-up with blood draw
Visit 8 (Day 168) - Clinic Follow-up with blood draw
Visit 9 (Day 196) - Clinic Follow-up with blood draw
Visit 10 (Day 224) - Clinic Follow-up with blood draw
Visit 11 (Day 252) - Clinic Follow-up with blood draw
Visit 12 (Day 280) - Clinic Follow-up with blood draw
Visit 13-Visit 26 (Days 224 - 672) - about 8 visits every one to two months - Clinic Follow-up with blood draw

At each visit, we will ask you about any health changes or problems. We will ask how you are feeling and if you have taken any medications. At scheduled clinic visits, we will draw about 2 to 9 tubes of blood from you, depending on the visit. Total blood taken from you during the 2 year study will be about 777 mL (approximately 53 tablespoons).

During screening we will collect up to 15 mL or 1 tablespoon of blood to check your complete blood counts (CBC) and perform a liver function test (ALT or alanine aminotransferase) and a kidney function test (Cr or creatinine).

On visits 2, 3, 4, 6 and 13 we will be collecting about half a tablespoon (about 7 mL) of blood to check your CBC and ALT. We will review the results with you before or at your next visit.

On visits 1, 2, 3, 4, 5, 6, 13, 20, and 26 we will also be collecting about 4-5 tablespoons (about 56-80 mL) of blood for your immune responses (your body's way of protecting itself). The other clinic follow-up visits we will collect about 1-1.5 tablespoons (about 18 mL) of blood for your immune responses. These tests are for the research.

If any of your lab test results show a health problem, we will tell you about it as soon as possible. You might need to have extra clinic visits and laboratory tests if you have health changes that we need to check.

On Vaccination Visits (Visits 2, 3, and 4)

If you are a female who is able to get pregnant, you will be given a pregnancy test before you get each product administration. The test must show that you are not pregnant before we can give you the study product.

We will watch you in the clinic for at least 15 minutes after you get each full dose of study product, which is after you get both injections.

We will ask you to complete a diary card for 7 days after each product administration. You will use the diary card to write down your highest temperature each day and any side effects that you feel. You will also need to look at the injection sites each day and write down how it looks and any side effects that you see. We will give you a thermometer and a measuring device to do this. We will ask you to review your diary card with us about a week later.

The clinic staff is available to you by phone 24 hours a day to report any unexpected side effects. If you have any concerning side effects or if you feel sick, you should tell the clinic right away. We may ask you to come into the clinic for an examination before your next scheduled visit. It is very important that you follow the instructions we give you.

Experimental vaccine studies like this one follow a set schedule. The study schedule for your visits allows some flexibility, but it is important that you work with the staff to follow the set schedule as much as possible. You should try to not miss any visits.

If you agree to take part in this study, it is important for you to keep all of your appointments.

If you get at least one injection, we will ask you to continue with your planned follow-up visits to monitor your health until the end of the study. It is important that we continue to check your health even if you do not get the second or third product administration.

Sample Collection for Zika Diagnosis

At any time during the study, if you think you have Zika infection, you must contact our clinic right away. We will ask you to come in for a clinical examination and we may collect blood and urine so that we can test you for Zika infection. We may also test for other infections that have symptoms similar to Zika infection. If you have a rash or another sign or symptom of illness that could possibly be a Zika infection, we may take a photograph of the affected area with your permission. These photographs will not identify you in any way and willonly be used by the study team to evaluate your illness.

These samples will be shipped to either the Primary Diagnostic Laboratory at the University of Washington (Seattle, WA, US) or the Diagnostic and Reference Laboratory Arbovirus Diseases Branch,

Centers of Disease Control and Prevention (CDC), (Fort Collins, CO, US) for testing.

We will tell you the results of your test(s) as soon as possible but it may take several weeks to get the results. It is very important that you get tested for Zika infection at our clinic only and that you do not get tested elsewhere unless it is necessary for your health, for example while traveling.

Sample Collection for Zika Research

Many people who have Zika infection do not feel sick even when there is virus in their blood, urine, or other bodily fluids. As part of this study, we will collect blood samples from you about once a month for the first year and then every two months for the whole study (which is 96 weeks) so we can test for Zika infection. The sample collection plans may change if you get Zika infection. We will collect these samples for research purposes only.

Voluntary Participation

Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time during the study. There is no penalty or loss of benefits for choosing to leave the study at any time.

Monitoring of the Study

This study will be monitored by a group of physicians and scientists associated with the United States NIH. This group will review the study information and will pay close attention to any reactions that people have to the study products.

Stored Samples

We will collect blood and other bodily fluids such as urine from you during this study. We will keep these samples to study your immune response to the study product and for future research to learn more about Zika, vaccines, the immune system or other related medical conditions. The urgency of the Zika epidemic has accelerated the development of Zika tests and assays. Samples from study subjects may be an important part in the development of new assays to diagnose and to study Zika infections. No genetic research (deoxyribonucleic acid [DNA] testing) will be done on these samples.

Research samples will be shipped to the Fisher BioServices (Germantown, MD, US) storage facility. Research samples may be stored for up to 20 years. Stored samples may be sent for testing by any of the following laboratories:

VRC/NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL; Rockville, MD, US)
NIAID Laboratory of Infectious Diseases (LID; Bethesda, MD, US)

Battelle, Biomedical Research Center (West Jefferson, OH, US)
Z-Quick/University of Miami Life Science and Technology Park (Miami, FL, US)
Blood Systems Research Institute (BSRI, San Francisco, CA, US)

As new tests are developed, additional laboratories may use your stored samples for testing. These laboratories are unknown at this time.

Results from the research done with your stored samples are not for diagnostic purposes or medical care. Therefore, the results will not be part of your medical record.

Labeling of Stored Samples

Your stored samples will be labeled by a special code or number that only the study team can link to you. Any identifying information about you, like your name or date of birth, will be kept as confidential as allowable by law. Despite protections, there is a small chance that information identifying you will be given to someone who should not get it.

Future Studies

In the future, other researchers at NIH or outside of NIH may wish to study your stored samples. When the study team shares your samples, they will be marked with a code. Your samples will not have any information on them that could identify you. Some information about you, such as your gender, age, health history, or ethnicity may be shared. Any future research done with your samples willbe done in a way that protects the rights and privacy of study subjects.

Your stored samples will be used only for research and will not be sold and stored at Fisher BioServices. The research done with your samples may be used to develop new products in the future but you will not get payment for these products.

By signing this consent form you agree to allow the samples to be stored for future research.

Human Data Sharing

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name, address, and birth date. The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

You may stop participating in this study at any time and withdraw permission for your individual data, specimens, and health information to be used for additional or future research. You may ask to have your research data destroyed. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning alcohol abuse
- Specific information concerning drug abuse
- Specific information concerning sickle cell anemia
- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Full Social Security #

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, and NIH: NATIONAL INSTITUTES OF HEALTH and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and

conducting public health surveillance, investigations or interventions.

Baylor College of Medicine is required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research does not involve treatment. Baylor College of Medicine may not condition (withhold or refuse) treating you on whether you sign this Authorization.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, NIH: NATIONAL INSTITUTES OF HEALTH and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: [redacted]

[redacted]

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts
Possible Risks from the Injections

Temporary stinging, pain, redness, soreness, itchiness, swelling, or bruising. Injections given with the needle-free device have been shown to cause a small cut at the injection site. A small scab may form within 1 to 2 weeks after the injection is given. There is a very small chance of infection.

There is also a small chance that the needle-free device could not work properly. As of July 2018, 0.54% of VRC 705 injections involved a PharmaJet device malfunction. This includes the syringe breaking and study product spraying during administration. No study subjects were harmed because of these malfunctions. However, because there is the possibility of a malfunction, we ask that you wear

safety glasses while we give the injections.

Possible Risks of Blood Drawing

Pain, bleeding, bruising, feeling lightheaded, or fainting, and rarely, infection at the site where blood is taken.

Possible Risks from any Vaccine

Fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired or unwell. Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after an injection and typically last 1 to 3 days. Medicines, such as acetaminophen, may be used to help relieve these symptoms.

Very rarely, a serious allergic reaction with symptoms such as hives, trouble breathing, or sudden weakness may happen shortly after any vaccination. This is called ¿anaphylaxis¿ and may be life-threatening. While you are waiting in the clinic after the injections, we will monitor you for anaphylaxis. Treatment for anaphylaxis will be given right away if it happens.

Possible Risks of DNA Vaccines

Temporary drop in white blood cell count, sore arm, skin rash or hives, some people get a small red bump and then a scab for a few days where the injection is given. The NIH has tested many similar vaccines made by the VRC and these vaccines were found to be safe and well-tolerated. We expect this vaccine to be like the ones tested before. However, no guarantee can be made that this vaccine will be as safe and well-tolerated.

Possible Risks of the Zika DNA Vaccine

As of July 2018, this Zika vaccine has been tested in 45 subjects in the Phase 1 study, VRC 320. The most common complaints after injection by PharmaJet are mild or moderate headache, feeling tired or unwell, and mild pain at the injection site.

A very similar Zika vaccine has been tested in 80 subjects in a previous study (VRC 319). As of July 2018, that experimental vaccine was found to be safe for additional studies in humans. So far, the most common complaints after injection by needle and syringe have been mild pain at the injection site, mild or moderate headache, muscle aches and feeling tired or unwell.

This Zika vaccine does not contain Zika virus. Guillain-Barré syndrome has not been seen with similar vaccines or vaccines made against similar viruses. We do not know if there is a risk of Guillain-Barré syndrome from the study vaccine. However, we have to be very cautious and observant with a Zika vaccine. This is because natural Zika infection seems to be associated with Guillain-Barré syndrome

and we don¿t know how Zika might cause Guillain-Barré syndrome. You should tell the study team if you develop weakness or tingling in your arms or legs or any other unusual symptoms.

Possible Risks during Pregnancy

We do not know if getting the study products will affect a fetus. Therefore, if you are a woman who can get pregnant you must agree to use an effective method of birth control starting at least 21 days before getting the first study product administration until 12 weeks after the last product administration. We will discuss effective birth control methods with you. If you are pregnant or want to become pregnant in the next 20 weeks, you cannot participate.

During the study, if you think you might be pregnant, you must tell the study staff right away. If you are pregnant, you will not get any more study product. We will give you resources you can use to learn about protecting yourself from getting Zika infection. You will be asked to continue with some follow-up visits. We will ask you about the outcome of the pregnancy.

Confidentiality

You will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see your PHI. All records will be kept in a locked file cabinet or maintained in a locked room in our research areas. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Organizations that may inspect and/or copy research records maintained at our research site for quality assurance and data analysis include groups such as National Institute of Allergy and Infectious Diseases (NIAID) and FDA.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Results of United States NIH-supported research studies may also be reported in medical journals, on the internet or at scientific meetings. These reports will not have information that can identify you.

In most cases, the United States NIH will not release any information about your research participation without your written permission. However, if you sign a release of information form, for example, for an insurance company, the insurance company gets information from your medical record. This information might affect (either positively or negatively) if the insurance company sells insurance to you.

Unknown Risks

We do not know if the study product will affect how you respond to any future Zika infection or Zika

vaccine that you may get in the future. There may be side effects from the study products, even serious or life threatening ones that we do not yet know about. We will tell you if we learn about any important new findings or serious side effects of the vaccine during the study that may change your mind about your willingness to continue participation.

You may not donate blood while taking part in this study. You may not donate blood for one year after the date of your last product administration.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

You will receive no direct benefit from your participation in this study. However, your participation may help the investigators better understand how we can protect people from Zika infection. This study is not designed to benefit you or to protect you from Zika infection. You and others may benefit in the future from the information that we learn from the study.

Alternatives

You may choose to not participate in this study.

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you do not follow study instructions or keep appointments, if you have a serious reaction to the study product, or if continuing in the study could hurt you) or because the entire study is stopped. The sponsor, investigator, FDA, or Institutional Review Board may stop the study at any time.

Subject Costs and Payments

You will not be asked to pay any costs related to this research.

You will be compensated for your time and effort as part of the research study:

Visit 1 - Screening visit - you will receive a voucher for $50 for completion of the visit
During the screening visit, if you do not qualify for the study based on review of your health prior to the blood draw then you will be compensated $25.

Once you are eligible and enroll in the study you will be compensated as follows:

Visits 2, 3, 4: Product Administration visits (Total $300)
$100 for each completed product administration visit
If it is decided that you will not receive vaccine at a product administration visit you will be compensated $50 for that visit.

Visits 2A, 3A, 4A: Scheduled Phone call visits (Total $60)
$20 for each scheduled phone call visit completed

Visits 5-26 Follow-up Clinic Visits with blood draw - about 16 visits (Total $800)
$50 for each scheduled follow-up clinic visit with blood draw completed
Visits 15,17,19, 21, 23, 25 have been removed as of you signing this consent

$30 for each clinic visit for urine sample collection completed to date (up to $450)
Urine sample collection visits will not occur anymore.

Total compensation: about $1,700 over 2 years (24 month) for completing screening visit and scheduled clinic/phone call study procedures/visits.

The total that you receive will be based on the number of study visits you complete and the number of product administrations you get. If you do not complete the whole study, you will be compensated only for the visits you have completed.

You will be compensated $50 for any unscheduled clinic visits that may be necessary to follow-up on your health during the study.

The compensation will be distributed at regular intervals during the conduct of the study by ClinCard.

Compensation for research participation are considered taxable income per Internal Revenue Service (IRS)regulations. If the total amount of payment received by you or your Legally Authorized Representative (LAR) reaches or exceeds $600 in a calendar year, Baylor College of Medicine (BCM) will send an IRS Form 1099 to that person for tax purposes.

To issue the IRS Form 1099, BCM will collect your name, social security number, date of birth and home

address. The name you provide should match the social security number. If you do not wish to provide a social security number, you can still participate in the study and decline all payment.

Please note study compensation is considered income and may or may not affect government or public assistance benefit programs you or your LAR may be participating in, such as SSI (Supplemental Security Income) or TANF (Temporary Assistance for Needy Families).

Compensation for study visits will be loaded onto the ClinCard within 48-72 hours of visit completion. The research study team will provide you with a handout about the ClinCard. Your email address and/or cell phone number will be collected in the event you want email or text notification when payments are loaded to your ClinCard. BCM and Greenphire (ClinCard Company) have entered into an agreement which requires Greenphire to protect your personal information.

BCM will replace your ClinCard free of charge if your first card is lost or stolen. After that, there is a $7 ClinCard replacement fee. This replacement fee will be charged to the balance on your ClinCard at the time of replacement. Your ClinCard has an expiration date. If your ClinCard expires while you are participating in this study, BCM will provide you with a new ClinCard at no cost to you. For a period of three months following your final study visit, you may request replacement of an expired ClinCard at no cost to you.

You will also be provided parking validation for the Texas Medical Center parking garages to cover parking expenses you may have during your study visits or reimbursement up to $12 for use of public transportation to and from our clinic visits.

Research Related Injury

The study site will provide immediate medical care for any injury resulting from you being in research here.

The study doctor will also provide referrals to appropriate health care facilities. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the study or the US NIH or the US Federal Government. However, by signing this consent form you do not give up any of the legal rights you have as a participant in a research study.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing

this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, [redacted] and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: [redacted] or her staff at [redacted] during the day and after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is ([redacted]. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

Your decision whether or not to participate will not affect your current or future relations with Baylor College of Medicine (BCM).

CONTACT FOR FUTURE STUDIES

We may want to contact you in the future to ask if you would like to participate in another study . If you agree, we would like to keep your name, date of birth, address, phone number, and e-mail address on file. This information will be kept secured and confidential and will not be shared with other investigators at this or other institutions.

Please INITIAL your decision about permission for us to contact you in the future for upcoming studies (indicate only ONE option):

_____YES, you may contact me in the future by telephone, e-mail, text messaging, or postal mail to inform me of upcoming studies.

_____NO, you may not contact me in the future regarding upcoming studies.

Agreeing to be in this study does not obligate you to participate in any of our future studies and a separate consent document would be signed for any future study.

FUTURE USE OF YOUR RESEARCH SAMPLE

_____ Please initial here to indicate that you understand that by signing this consent form and participating in this study that you agree that your research samples in this study will be stored for future research as explained in this consent form.

ASSESSMENT OF UNDERSTANDING

Before the first time you screen for this study and you sign this consent form we will ask you to complete a questionnaire with 20 True/False questions (an Assessment of Understanding) which is a tool to help make sure you understand the research that you may agree to be part of. You do not have to get all the questions correct, but if you miss any questions the study staff will review the question and the correct answer with you to make sure you understand the research study.

TIME OF CONSENT SIGNATURE: _____ (CIRCLE ONE) AM / PM

SUBJECT INITIALS: _____

H-40208- A PHASE 2/2B, RANDOMIZED TRIAL TO EVALUATE THE SAFETY, IMMUNOGENICITY AND EFFICACY OF A ZIKA VIRUS DNA VACCINE IN HEALTHY ADULTS AND ADOLESCENTS (VRC 705 VER 5.0 28AUG2018)

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date

STATISTICAL ANALYSIS PLAN

for

Protocol VRC 705

Study Title:

A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika Virus DNA Vaccine in Healthy Adults and Adolescents

ClinicalTrials.gov Registration:
NCT03110770

Version 1.0
DATE: November 11, 2019

STUDY TITLE

Protocol Number Code:	Protocol VRC 705
Development Phase:	Phase 2/2B
Products:	VRC-ZKADNA090-00-VP (ZIKVwt DNA vaccine) VRC-PBSPLA043-00-VP (sterile phosphate-buffered saline)
Form/Route:	IM administration via PharmaJet Stratis® 0.5 mL Needle-Free Jet Injector (PharmaJet)
Indication Studied:	Zika virus
Sponsor:	Vaccine Research Center
Clinical Trial Initiation Date:	Part A: March 29, 2017 Part B: July 19, 2017
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	November 11, 2019
Version Number:	1.0

TABLE OF CONTENTS

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ATC	Anatomical Therapeutic Classification
CI	confidence interval
DENV	dengue virus
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
ELISA	enzyme-linked immunosorbent assay
ELISpot assay	enzyme-linked immunospot assay
FDA	United States Food and Drug Administration
GBS	Guillain-Barré syndrome
GEE	generalized estimating equation
GMFI	geometric mean fold increase
GMT	geometric mean titer
H0	null hypothesis
HIV	human immunodeficiency virus
HR	Hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IM	intramuscular
IND	investigational new drug
ITT	Intent-to-treat
MedDRA®	Medical Dictionary for Regulatory Activities
MCV	mean corpuscular volume
mITT	modified intent-to-treat
NAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NCMC	new chronic medical condition
NVITAL	NIAID Vaccine Immune T-Cell and Antibody Laboratory
PAHO	Pan American Health Organization
PBS	phosphate-buffered saline
PCR	polymerase chain reaction

List of Abbreviations *(continued)*

Abbreviation	Term
PDL	primary diagnostic laboratory
PI	Principal Investigator
PP	per protocol
PSRT	Protocol Safety Review Team
PT	preferred term
RNA	ribonucleic acid
RVP	reporter virus particle
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System organ class
TBD	to be determined
TFL	tables, figures, and listings
US	United States
VE	vaccine efficacy
VRC	Vaccine Research Center
WBC	white blood cell
WHO	World Health Organization
WNV	West Nile virus
ZIKV	Zika virus
ZIKVwt	Zika virus wild-type

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 2/2B, Randomized Trial to Evaluate the Safety, Immunogenicity and Efficacy of a Zika virus DNA Vaccine in Healthy Adults and Adolescents" (VRC 705) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses that will be conducted by the VRC 705 Data Center and provides reasons and justifications for these analyses. It also includes sample tables, figures, and listings (TFL) planned for the final analyses. Regarding the final analyses, this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety endpoints, and (4) a list of proposed TFLs (Appendices 1, 2, and 3).

Following any protocol amendment, this SAP will be reviewed and revised to address any changes in the protocol impacting analysis. Any deviation from the final SAP will be described and justified. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

The Dale and Betty Bumpers Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) (Bethesda, MD, USA) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies to provide safe and effective means to prevent and control infectious diseases. Zika virus (ZIKV) is a mosquito-borne infection causing illness with mild symptoms including fever, rash, joint paint and conjunctivitis that may last for several days to weeks.

Since its discovery in Uganda in 1947, outbreaks of ZIKV have been reported in Africa, Southeast Asia, and the Pacific Islands. ZIKV emerged in Brazil in 2015 and then rapidly spread throughout the Americas [1]. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed ZIKV infection in Brazil and on February 1, 2016, the World Health Organization (WHO) declared ZIKV a public health emergency of international concern due to evidence suggesting ZIKV infection may be linked to recent clusters of microcephaly in babies born to infected mothers and other reported neurological disorders including Guillain-Barré syndrome (GBS) [2]. According to the WHO, local transmission has now been reported in many other countries and territories and will continue to spread to new areas.

There are currently no effective vaccines or therapies against ZIKV. The rapid emergence of ZIKV supports the need for a safe and immunogenic vaccine. This protocol is designed as a Phase 2B evaluation of the investigational ZIKV DNA vaccine, VRC-ZKADNA090-00-VP. This candidate vaccine was evaluated in a Phase 1 study (VRC 320, NCT02996461).

VRC 705 is a multicenter, randomized, clinical trial evaluating the safety, immunogenicity, and efficacy of a three-dose vaccination regimen with the Zika virus (ZIKV) wild-type (ZIKVwt) DNA vaccine, VRC-ZKADNA090-00-VP. This Phase 2/2B study is being advanced rapidly to follow the initiation of the Phase 1 studies due to the significant public health need for a vaccine to prevent ZIKV. The study includes two Parts: **Part A** is an open-label evaluation of 90 subjects randomized to one of 3 groups to receive a 4 mg or 8mg dose of vaccine split between 2 or 4 injections; **Part B** is a double-blinded evaluation of 2400 subjects randomized to receive ZIKV vaccine or placebo.

2.1. Purpose of the Analyses

Note, not all analyses for endpoints included in the protocol are detailed in this plan. The exploratory endpoint analyses are not included in this SAP.

In **Part A**, the primary objective is to evaluate the safety and tolerability of the vaccine. In **Part B**, the primary objectives are to evaluate the safety and efficacy of the vaccine compared to the placebo. Secondary and exploratory objectives of the study relate to immunogenicity and durability of immune responses.

The VRC 705 protocol calls for multiple planned interim analyses. During **Part A** of the study immunogenicity may be analyzed in an ongoing fashion. During **Part B** of the study the following interim analyses will be performed:

1. **Interim immunogenicity analyses** may be performed after the neutralizing antibody (NAb) assays up to and including Week 12 have been completed on a subset of subjects.
2. **Interim efficacy analysis** may be performed when the total number of ZIKV cases in the modified Intent-to-treat (mITT) cohort reaches 30 and 60.

For **Part B**, the final efficacy analysis will occur when the total number of virologic ZIKV cases in the mITT cohort reaches 90 or study completion. The final analysis of **Part A** and **Part B** will be performed and completed when all primary and secondary safety, efficacy, and immunogenicity endpoint data are available, and the study database has been locked. The study clinical database and immunogenicity/efficacy database will be locked separately; the final analysis of **Part A** and **Part B** safety data will follow the clinical database lock and the final analysis of **Part A** and **Part B** immunogenicity and efficacy data will follow the second database lock once all lab data are received and validated.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Refer to Protocol Section 3, "Study Objectives."

3.2. Endpoints

Refer to Protocol Section 6.2, "Endpoints."

3.2.1. Study Definitions and Derived Variables

The baseline value will be defined as the last value obtained prior to the receipt of the first product administration on Day 0 (Visit 02).

Individual neutralization antibody (NAb) assay results will be reported as a titer. Fold-rise (NAb) is a measure that describes how much the NAb titer changes from an initial to a final value. The fold-rise is calculated as the ratio of the final value to the initial value. Subjects will be tested for baseline ZIKV serostatus based on serum samples collected at screening, Visit 01.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

Refer to Protocol Precis.

4.2. Discussion of Design, Including the Choice of Control Group

Refer to Protocol Section 4, "Study Design and Clinical Procedures."

4.3. Selection of Study Population

Refer to Protocol Precis.

4.4. Study Product Administrations

4.4.1. Study Product

Refer to Protocol Section 2, "Study Products".

4.4.2. Vaccine Dose and Administration Method

Refer to Protocol Section 1.5, "Rationale for Study Product Dose and Administration Method."

4.4.3. Method of Assigning Subjects to Study Groups (Randomization)

Refer to Protocol Section 6.4.6, "Randomization of Treatment Assignments and Unblinding Criteria."

4.4.4. Blinding and Conditions for Unblinding

Refer to Protocol Section 6.4.6, "Randomization of Treatment Assignments and Unblinding Criteria."

Please refer to the Study Blinding Plan for additional details on blinding and processes for planned and unplanned unblinding events.

5. SAMPLE SIZE CONSIDERATIONS

Refer to Protocol Section 6.3, "Sample Size and Accrual."

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Summary tables will be presented separately for **Part A** and **Part B**, and will mostly be structured with columns summarizing the groups as follows:

Part A

- Group 1: 4 mg ZIKVwt DNA, 2 injections
- Group 2: 4 mg ZIKVwt DNA, 4 injections
- Group 3: 8 mg ZIKVwt DNA, 4 injections
- All Part A Subjects.

Since the primary safety objective indicates assessing the 4mg dose regardless of the number of injections, safety data will be tabulated with the following columns.

- Group 1: 4 mg ZIKVwt DNA, 2 injections
- Group 2: 4 mg ZIKVwt DNA, 4 injections
- Groups 1 + 2: 4mg ZIKVwt DNA, 2 or 4 injections
- Group 3: 8 mg ZIKVwt DNA, 4 injections
- All Part A Subjects.

Part B

- Group 4: 4 mg ZIKVwt DNA
- Group 5: Placebo
- All Part B Subjects.

The total sample size for each summary group for the applicable analysis population being tabulated will be displayed in all tables.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean (or geometric mean, as appropriate), standard deviation, median, minimum and maximum. The frequency and percentages (denominators based on the non-missing sample size) of observed levels will be reported for all categorical measures. Unless otherwise specified, Clopper-Pearson exact methodology will be used to calculate CIs for proportions. All logarithmic transformations will be done using the natural log.

In presenting statistical inferences, the statistical claim (i.e. null and alternative hypotheses) will be clearly stated, the method used for hypothesis testing or CI estimation will be described and appropriately referenced, and the assumptions underlying the methods will be validated.

All data will be included in listings, sorted by study group and subject, and when appropriate by administration number and/or visit number within subject. Listings will be presented with **Part A** and **Part B** data separated.

6.2. Timing of Analyses

1. **Interim immunogenicity analyses** for **Part A** may be performed on an ongoing basis, per sponsor directive.
   a) The first interim immunogenicity analysis will be performed when 10 subjects in each group have data available through Visit 05
2. **Interim immunogenicity analyses** for **Part B** may be performed on a subset of subjects after the NAb assays up to and including Week 12 have been completed for the subset of subjects.
3. **Final Efficacy Analysis** will occur when the total number of mITT virologic ZIKV cases (primary efficacy endpoint) in **Part B** of the study reaches 90 or study completion.
4. The **Final Analysis** of safety data for both Part A and Part B will be performed after clinical database lock when all subjects have been followed through 32 weeks after the last product administration for Part A and at least 6 months after the first product administration for Part B. Final analysis of the efficacy and immunogenicity endpoint data will follow the database lock of the immunogenicity and efficacy data once all lab data are received and validated.
5. **Exploratory Immunogenicity Analyses** may be completed following database lock as assay results become available.

For all analyses completed prior to database lock, individual subjects' study group assignments will not be unblinded with the possible exception of a review of selected AEs or episodes of ZIKV disease for safety monitoring requirements, as described in the Study Blinding Plan.

6.3. Analysis Populations

The two parts of the study share the following definition for each type of analysis population:

All Enrolled Subjects: all subjects who enrolled in the screening segment. This population will be used for summaries of subject disposition, eligibility, demographics and the serious adverse event listing.

Safety population: all randomized subjects in the study who receive at least one study product administration, and have at least one post-administration safety assessment, analyzed according to the study product received. If it is unknown what study product was received, subjects will be summarized according to the randomized treatment assignment. This population will be used for analysis of all safety endpoints.

The **Intent-to-treat (ITT)** population will include all randomized subjects, analyzed according to the randomized study product. The ITT population will be used to analyze immunogenicity and efficacy analyses.

The **Modified intent-to-treat (mITT**) analyses will include all randomized subjects who remain event-free one week after all planned product administrations, where event is the primary efficacy event of a positive ZIKV PCR or other Zika test result with or without symptoms, analyzed according to the randomized study product. The mITT population will be used for immunogenicity and efficacy analyses (**Part B** only).

The **Per Protocol (PP)** analyses will include all subjects receiving three administrations within window as assigned by the randomization schedule, and not experiencing any other major protocol deviations prior to their week 12 visit. Safety, immunogenicity, and efficacy analyses will all be examined for the PP population. The following subjects will be excluded from the PP population:

- Subjects who do not receive 3 administrations of study product.
- Subjects who acquire confirmed ZIKV infection on or before 1 week after third administration.
- Subjects missing baseline ZIKV serostatus.
- Subjects who received a study product administration different from the randomization assignment.
- Subjects who receive the second or third administration out of the protocol-defined windows:
- Subjects who did not meet all inclusion/exclusion criteria at the time of enrollment.
- Subjects whose study group assignment is unblinded during study follow-up (**Part B**).
- Subjects who receive study product via incorrect route or incomplete administration.
- *For efficacy analyses* – subjects who do not have at least one post-administration efficacy assessment (at least one visit or PCR (or other Zika) result) following product administration 3.
- *For immunogenicity analyses* – subjects who do not have NAb results 4 weeks post product administration 3 (Visit 05) or at baseline.
- *For immunogenicity analyses* – subjects with serum sample for 4 weeks post product administration 3 (Visit 05) collected outside the protocol specified window (Day 77 to Day 91).

Subjects may be censored from the Per-Protocol Analysis for any of the following:

- Receipt of any non-study inactivated vaccination within 2 weeks of any study product administration.
- Receipt of any live attenuated vaccination within 4 of any study product administration.

- Receipt of any other investigational research agent at any time during the trial.
- Receipt of any concomitant medication that may interfere with immune response, including but not limited to:
    - Any systemic immunosuppressive or cytotoxic medical blood products within 16 weeks prior to randomization.
    - Immunoglobulin within 8 weeks prior to randomization.
    - Current anti-TB prophylaxis or therapy.
- Confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.

All exclusions from analysis populations and censoring events will be reviewed by the Protocol Statistician, Protocol Chairs, and Lead Medical Officer and others on the Protocol Safety Review Team.

6.4. Covariates and Subgroups

All immunogenicity analyses will be conducted overall and stratified by baseline ZIKV seroprevalance for all Part A and Part B subjects. Additional summaries may be tabulated by clinical site, but the study is not powered for any additional subgroup analyses.

6.5. Missing Data

Missing data will be primarily considered as missing completely at random in safety and immunogenicity analyses provided missing data is modest (e.g. <10%). For completeness, we will examine the missing data completely at random assumption and perform sensitivity analyses which weaken the missing completely at random assumption if the missing data is >10% or if the missing at random assumption is questionable. Data will be presented as available; no imputation is planned. For efficacy, missing at random will be assumed and imputation may be implemented if supported by the data and if sufficient consequence to justify their inclusion.

6.6. Interim Analyses and Data Monitoring

6.6.1. Independent Safety Reviews

The Protocol Safety Review Team (PSRT) will review safety data routinely throughout the study. The study will utilize both electronic database features and reviews by designated safety review personnel to identify in a timely manner if any of the safety pause rules of the study are met. The NIAID Data and Safety Monitoring Board (DSMB) will provide an independent safety review at scheduled intervals to coincide with their biannual meeting schedule.

6.6.2. Immunogenicity Reviews:

Part A: The data in Part A will be used in an ongoing manner to help select the regimen to be used in Part B. Analyses will be performed as described in Section 9.

Part B: An interim analysis of immunogenicity data may be performed after the NAb assays up to and including Week 12 have been completed on a subset of subjects. Analyses will be performed as described in Section 9. Reports will be provided to the Protocol Chairs and other key investigators as described in the study blinding plan solely for the purpose of informing future trial-related decisions in a timely manner. Results will be provided summarized by treatment arm, and to prevent inadvertent unblinding, no individual subject data will be released that would indicate study group. The results will remain confidential and should in no way influence the conduct of the VRC 705 trial in terms of early termination or later safety or immunogenicity endpoint assessments.

6.6.3. Incidence Reviews (Part B only):

The study will be regularly monitored using the combined (blinded) incidence rates for ZIKV disease and for ZIKV infections. These rates will be monitored at each site and over all sites combined. Such monitoring will allow for enrollment to be expanded or curtailed at different sites.

Prior to completion of enrollment of the 2400 Part B subjects, calculations using the blinded incidence rates will be performed to estimate the expected time to achieve 90 cases of ZIKV disease. Based on these calculations, the sample size may remain fixed at 2400, be increased up to 15,000, or the trial may be stopped for lack of feasibility if this expected time is deemed excessive.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for study product administration and assessment of solicited and unsolicited AEs, and the study relies on central laboratories for the assessment of immunogenicity and clinical efficacy endpoints.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A summary of the reasons why subjects were screened but not randomized will be presented overall in Table 1 and by site in Table 2 **(Appendix 1).** The disposition of subjects in the study will be tabulated by study group (Table 3 for **Part A and** Table 4 for **Part B, Appendix 1**) and by site (Table 5 for **Part A and** Table 6 for **Part B, Appendix 1**). The tables will display the total number and percentage of subjects screened, randomized, received the first administration, received the second administration, received the third administration, terminated from study follow-up, and completed the protocol.

The number of subjects included in each analysis population, and the number meeting each population exclusion criterion, will be presented in Table 7 for **Part A** and in Table 8 for **Part B (Appendix 1).**

A flowchart showing the disposition of study subjects, adapted from the CONSORT Statement [3] will be included **(**Figure 1 for **Part A** and Figure 2 for **Part B, Appendix 2).** This figure will present the number of subjects screened, randomized, vaccinated, and included in the mITT and PP analysis populations by study group.

A listing of subjects who discontinued dosing or terminated from study follow-up and the reason will be included in Listing 1 and Listing 2 **(Appendix 3).**

A listing of subjects who were unblinded during study follow-up will be included in Listing 4**.**

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation and the deviation category for all enrolled subjects **(**Table 9 for **Part A,** Table 10 for **Part B,** Table 11 for **Screening Segment, Appendix 1).** Deviations will be reviewed for possible subject exclusion from the per protocol population including those defined in Section 6.3. All subject-specific protocol deviations, non-subject-specific protocol deviations, and unanticipated problem reports will be included in in data listings (Listing 3**,** Listing 4**,** Listing 5**,** Listing 6**,** Listing 7**, Appendix 3)**.

8. SAFETY EVALUATION

8.1. Demographic and Other Baseline Characteristics

Summaries of age, gender, ethnicity, race, and language will be presented by study group for all enrolled subjects, the mITT population, and the ITT population **(**Table 13 **-** Table 14 **,** for **Part A** and Table 15 **-** Table 16**, Part B, Appendix 1)**, and by site for all enrolled subjects **(**Table 17 for **Part A** and Table 18 for **Part B, Appendix 1).**

Ethnicity is self-reported by subjects as Mexican, Mexican-American, or Chicano/a; Puerto Rican; Cuban; Another Hispanic, Latinola, or Spanish origin; Not of Hispanic, Latinola or Spanish Origin; Unknown/Not Reported. Ethnicity will be summarized as categories of Any Hispanic, Latinola, or Spanish Origin, or Not of Hispanic, Latinola or Spanish Background.

In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option. The race categories collected on the eCRF: White; Black or African American; American Indian or Alaskan Native; Asian Indian; Chinese; Filipino; Japanese; Korean; Vietnamese; Other Asian; Native Hawaiian; Guamanian or Chamorro; Samoan; Other Pacific Islander. Race may also be presented with categories aggregated such that any categories reported by <5% of subjects are reported as "Other".

Individual subject listings will be presented for all demographics **(**Listing 10 **-** Listing 11 **, Appendix 3)**.

8.1.1. Concurrent Illnesses and Medical Conditions

All current illnesses and past or pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 20.0 or higher.

Summaries of subjects' pre-existing medical conditions will be tabulated by system organ class (SOC) and preferred term (PT) (Table 19 for **Part A** and Table 20 for **Part B, Appendix 1**).

Individual subject listings will be presented for all medical conditions **(**Listing 12 **-** Listing 13**, Appendix 3**).

8.1.2. Prior and Concomitant Therapy

Only routine prescription medications will be entered in the database at the time of study randomization. All approved vaccinations for routine health care will be entered in the database throughout the study. Concomitant medications will be updated in the study database if there is an occurrence of an AE that requires expedited reporting or development of a new chronic medical condition that requires ongoing medical management. Otherwise, concomitant medications taken throughout the study will be recorded in the subject's chart, including any medication taking for DENV infection.

Individual subject listings will be presented for all concomitant medications (Listing 38 - Listing 39, **Appendix 3**).

8.2. Measurements of Treatment Compliance

In both parts of the study, all subjects are to receive 3 doses of study product administered in the clinic. The number of doses of study product administered to subjects will be presented by study group and by site as part of the subject disposition table as described in Section 7.1**.**

8.3. Adverse Events

When calculating the incidence of AEs (i.e., on a per subject basis), each subject will only be counted once and any repetitions of AEs within a subject will be ignored.

8.3.1. Solicited Events and Symptoms

Solicited AEs will be recorded in the study database separately with data collection on the day of administration and for 7 days after each product administration, graded on a scale of 0 (none), 1 (mild), 2 (moderate) and 3 (severe), without the collection of attribution assessments. The solicited signs and symptoms on the diary card will include the following parameters: malaise (unusually tired/feeling unwell), myalgia (muscles aches (other than at injection sites), headache, chills, nausea, joint pain, and pain/tenderness at the injection sites. Subjects will also record the highest measured temperature per day and measurement per day of the largest diameter for redness and swelling at the injection sites, if applicable. Subjects are instructed to record the greatest local symptoms or measurement when evaluating multiple injection sites. Subjects will be provided with devices to measure temperature and diameter.

The number and percentage of subjects reporting at least one solicited event of any severity following any administration will be summarized for each solicited symptom, any systemic symptom, any local symptom, and any solicited symptom. The denominator is the number of subjects in the Safety Analysis Population with non-missing data for the symptom being summarized. The 95% CI along with p-values from a Chi-square test comparing treatment groups will be presented **(**Table 60 for **Part A** and Table 61 for **Part B, Appendix 1)**. In cases where there is a small sample size (e.g. Part A), Fisher's exact 2-tailed test will be presented.

For each type of reactogenicity sign and symptom, the maximum severity (none, mild, moderate, severe, or missing) reported on Day 0 through Day 7 after each administration will be summarized. Similarly, the maximum severity across all systemic events and across all local events will be summarized. The number and percentage of subjects reporting each type of event, any systemic event, and any local event will be summarized by the maximum severity for each study group separately for each administration and over all administrations. **(**Table 62 for **Part A** and Table 63 for **Part B, Appendix 1)**.

The number of subjects reporting each type of solicited adverse event will be summarized for each day post administration by study group for each administration graphically in a bar chart **(**Figure 45 and Figure 47 for **Part A** and Figure 46 and Figure 48 for **Part B, Appendix 2)**.

Solicited adverse events reported for each subject who reported at least one mild or greater event will be presented in Listing 22 **-** Listing 23 for systemic adverse events and Listing 24 **-** Listing 25 for local adverse events**, Appendix 3.**

8.3.2. Unsolicited Adverse Events

Unsolicited AEs and their relationship to study product are recorded in the study immediately after the first product administration at Visit 02 through the one month visit that follows the last product administration. If a subject only receives the first product administration at Visit 02 but not the second or third, then the AE Reporting Period for unsolicited AEs and their relationship to study product is immediately after Visit 02 through Visit 03. If a subject only receives the first and second product administrations at Visit 02 and Visit 03, respectively, but not the third, then the AE Reporting Period for unsolicited AEs and their relationship to study product is immediately after Visit 02 through Visit 04. After this period, only SAEs, new chronic medical conditions, and confirmed cases of DENV will be recorded as an AE through the last study visit. SAEs are recorded from the time the informed consent is signed (Visit 01) through the end of the study.

The severity of an adverse event (AE) is reported on the eCRF as: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-threatening), and Grade 5 (Death). For any subject, only the single AE that is assessed as the primary cause of death should be assigned “Grade 5” severity. Following conventions of Clinical Data Interchange Standards Consortium (CDISC), conventions the severity data will be mapped to categories of Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), where any AEs reported on the eCRF as Grade 4 (Life-threatening) or Grade 5 (Death) will be coded as Grade 3 (Severe). The CDISC compliant severity grading scale will be used for all summaries and analysis for the final analysis.

Relation of an AE to the study product is defined as Definitely Related, Probably Related, Possibly Related, and Not Related. Following CDISC conventions the AE attributions will be mapped to “Related” or “Not Related”, where any AEs reported on the eCRF as “Definitely, Probably and Possibly” attributions will be mapped to the “Related” category. The CDISC compliant relationship will be used for all summaries and analysis for the CSR.

AEs will be coded into Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

Any SAEs reported before the first study product administration receipt at Visit 02 will be listed in Table 72**,** Table 78**,** Table 84**, Appendix 1**. All other tables and figures of unsolicited AEs will include only AEs reported following the first study product administration.

The number and proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA SOC and PT by study group for each study product administration and

over all study product administrations. Denominators for percentages are the number of subjects in the Safety Analysis Population who received the administration being summarized **(**Table 73**,** Table 74**,** Table 75 for **Part A** and Table 76**,** Table 77 for **Part B, Appendix 1)**. For each MedDRA system organ class and preferred term a 95% CI will be presented, along with the p-value for the comparison of study groups from a Fisher's exact test for **Part A** and a Chi-square test for **Part B (**Table 64**,** Table 65**,** Table 66**,** Table 67 for **Part A** and Table 68**,** Table 69**,** Table 70**,** Table 71 for **Part B, Appendix 1).**

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term for each administration and overall administrations, for all subjects:

- Proportion of subjects reporting adverse events by severity **(**Table 64 through Table 78**, Appendix 1);**
- Proportion of subjects reporting related adverse events by severity **(**Table 79 through Table 84**, Appendix 1);**
- Proportion of subjects reporting related adverse events by dose **(**Table 85 through Table 89**, Appendix 1);**
- Number of adverse events by dose **(**Table 90 through Table 94**, Appendix 1);**
- Number and proportion of subjects experiencing adverse events above 5% frequency threshold by MedDRA SOC and PT **(**Table 95 **-** Table 96**, Appendix 1);**
- Bar chart of the proportion of subjects reporting any adverse events by severity **(**Figure 49 **-** Figure 50**, Appendix 2);**
- Bar chart of adverse events by severity and MedDRA SOC for SOCs reported by 5% or more of subjects **(**Figure 53 **-** Figure 54**, Appendix 2);**
- Bar chart of adverse events by relationship to study product **(**Figure 51 **-** Figure 52**, Appendix 2);**

Unsolicited AEs by subject will be presented in Listing 26 through Listing 28**, Appendix 3.**

8.4. Deaths, Serious Adverse Events and other Significant Adverse Events

8.4.1. Deaths and Serious Adverse Events

A listing of Deaths will be presented including Subject ID, Age (years), Baseline ZIKV serostatus, Adverse Event Description, SOC, PT, Adverse Event Onset Date/End Date, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days).

A listing of SAEs will be presented including Subject ID, Age (years), Baseline ZIKV serostatus, Adverse Event Description, SOC, PT, Adverse Event Onset Date/End Date, Last Dose

Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days) **(**Table 99 for **Part A;** Table 100 for **Part B;** Table 101 for **Screening Segment, Appendix 1).** The number and proportion of subjects reporting at least one SAE will be summarized by MedDRA SOC and PT for each over all administrations (Table 98**, Appendix 1**).

8.4.2. New Chronic Medical Conditions

NCMC will be recorded on the AE form through the full duration of the study. These events will be identified from the database as any event without an end date and a date of onset greater than 28 days after the last product administration or any SAE at the time of trial completion. A blinded listing will be reviewed by the Protocol Lead Medical Officer prior to database lock. A listing of NCMC will be presented including Subject ID, Age (years), Baseline ZIKV serostatus, Adverse Event Description, SOC, PT, Adverse Event Onset Date/End Date, Last Dose Received/Days Post Dose, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days) **(**Table 104 for **Part A** and Table 105 **for Part B, Appendix 1).**

8.4.3. Confirmed Cases of DENV (Part B)

For **Part B**, confirmed cases of DENV will be recorded on an AE Form throughout the full duration of the study. The incidence of DENV will be summarized as the number and percentage of subjects tabulated by treatment arm overall and stratified by baseline ZIKV Status. 95% CIs will be included along with p-values from Chi-Square test (Table 107**, Appendix 1**).

8.5. Pregnancies

Female subjects of childbearing potential will receive pregnancy prevention counseling throughout the study. Women will be asked to notify the site immediately if they suspect or learn they are pregnant during this study. In case of pregnancy, subjects will be removed from the product administration schedule but may have limited clinic contacts and blood draws at the discretion of the site PI and IND Sponsor. The pregnancy outcomes are captured by the Pregnancy eCRF.

A table summarizing the total pregnancies, number of live births, miscarriages, elective abortions, ectopic pregnancies, still births, congenital anomalies, and neonatal deaths by treatment will be presented (Table 108 for **Part A**, Table 109 for **Part B**, **Appendix 1**). In addition, a listing of pregnancies and outcomes will be presented (Listing 40 for **Part A** and Listing 41 for **Part B, Appendix 3**).

8.6. Clinical Laboratory Evaluations

Planned safety laboratory parameters include: alanine aminotransferase (ALT), white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), platelets, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Laboratory safety evaluations are scheduled at baseline and weeks 4, 6, 8, 10, 12, 16 for **Part A**, and at baseline and weeks 4, 8, 16, 20, for **Part B**.

Only results for planned parameters and scheduled visits will be included in summaries. Safety laboratory evaluations are graded as follows: mild (grade 1), moderate (grade 2), severe (grade 3), or partially life threatening (grade 4) following the grading criteria in Protocol Appendix IV. Any abnormal laboratory results are reported as unsolicited AEs, and thus summarized as described in Section 8.3.2.

Safety laboratory results will be summarized for each parameter by study visit and study group. Continuous summary statistics for each parameter along with standard deviation for the mean will be presented in Table 117 through Table 119 for **Part A** and Table 120 - Table 121 for **Part B** (**Appendix 1**). Box plots for each parameter will be included in Figure 55 through Figure 66 for **Part A** and Figure 67 through Figure 78 for **Part B** (**Appendix 2**). Each boxplot will show the 1st quartile, the median, and the 3rd quartile, with values smaller than the 1st quartile or larger than the 3rd quartiles plotted as outliers. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

Continuous summary statistics for the change from baseline for each parameter along with standard deviation for the mean will be presented in Table 117 through Table 119 for **Part A** and Table 120 - Table 121 for **Part B** (**Appendix 1**). Each Safety laboratory parameter will be summarized using shift tables to compare baseline and follow-up values (Table 122 through Table 147 for **Part A** and Table 148 through Table 166 for **Part B**, **Appendix 1**). Shift tables will be analyzed using Generalized Estimating Equations (GEE) to account for the longitudinal nature of these data, as follows:

1) **For laboratory parameters with two categories: Normal and abnormal (Binary response) -**
   a. For each parameter the shift table displays the number of subjects categorized as normal and abnormal at baseline cross tabulated with normal and abnormal results at the post-product administration visit.
   b. A GEE for the binary responses above is fitted and used for parameter estimation
      - Observation (y_{ij}, X_{ij}) for each subject $i = 1, \dots, n$ and repeated measurement time point $j = 1, \dots, J$
      - dependent variable $y_{ij} = \begin{cases} 1 & abnormal \\ 0 & normal \end{cases}$, independent variable $X_{ij} = (group_{ij}, time_{ij}, group_{ij} * time_{ij})$;
      - probability of abnormal is $p_{ij} = \Pr(y_{ij} = 1)$;
      - model: $g(p_{ij}) = X'_{ij}\beta$ using the logit link;
      - GEE: $\sum_{i=1}^{n} \left(\frac{\partial P_i}{\partial \beta}\right) V_i^{-1}(\alpha)(Y_i - P_i)$=0 where $V_i(\alpha)$ is the working covariance matrix;
      - Implementation: PROC GENMOD (SAS) using SUBJECT option in the REPEATED statement to identify the cluster variable

- Output: point estimates and 95% CI for the individual levels of the GROUP, TIME and GROUP*TIME variables, and Type-3 SAS output for the parameter significance;
- Other analysis and outputs: Odds ratio with associated 95% CI of observing abnormality (from the fitted logistic model). Implemented with LSMEANS statement in PROC GENMOD.

2) **For laboratory parameters with three categories: Low, Normal and High (Ordinal response)**
   a. For each parameter the shift table displays the number of subjects who are categorized as low, normal, or high at baseline cross tabulated with low, normal or high results at the post-vaccination visit.
   b. A GEE model for the ordinal responses above is fitted and used for parameter estimation
      - Observation (Y_{ij}, X_{ij}) for each subject $i = 1, \dots, n$ at time point$j = 1, \dots, J$. $Y_{ij} = (y_{ij1}, y_{ij2})$ is the ordinal response variable with 3 ordered categories;
      - Cumulative probability $p_{ijk} = \Pr(y_{ijk} = 1: in\ lower\ k\ category) = \Pr(Y_{ij} \leq k), k = 1,2$;
      - Proportional Odds model $\begin{cases} g(p_{ij1}) = \mu_1 + X'_{ij}\beta \\ g(p_{ij2}) = \mu_2 + X'_{ij}\beta \end{cases}$ using the logit link;
      - $X'_{ij}\beta = \sim\beta_1 t_{ij} + \beta_2 group_{ij} + \beta_3 t_{ij} * group_{ij}$
      - GEE: $\sum_{i=1}^{n} \left(\frac{\partial P_i}{\partial \beta}\right) V_i^{-1}(\alpha)(Y_i - P_i)$=0 where$P_i = E(Y_i)$ $V_i(\alpha)$ is the working covariance matrix;
      - Output: estimates of two intercepts from the two fitted logistic models; point estimates and 95% CI for the individual levels of the GROUP, TIME and GROUP*TIME variables, and Type-3 SAS output for the parameter significance (chi-Square test);

The study is not powered to detect differences by study group, therefore the absence of statistically significant differences should not be interpreted as no such differences exist.

Individual clinical laboratory results will be presented for subjects with abnormal results of Grade 2 or higher for at least one parameter from at least one visit, including planned parameters collected at scheduled visits as well as any other parameters collected, and any results for unscheduled visits in Table 167 for **Part A** and Table 168 for **Part B, Appendix 1.**

8.7. Vital Signs and Physical Evaluations

Vital signs measurements include oral temperature, pulse, systolic and diastolic blood pressure, and respiratory rate. The assessment of vital signs is planned at baseline and weeks 4, 6, 8, 18, 12, and 16 for **Part A,** and at baseline and weeks 4, 8, 16, 44, 72, and 96 for **Part B**. Vitals are collected

pre- and post-study product administration. Vitals are also captured on the Visit Documentation eCRF at visits 6, 13, 20 and 26. A targeted physical exam is conducted at the same time points as the vital signs assessment and recorded in the subject's chart but not reported in the study database.

Vital signs will be summarized for each parameter by study visit, assessment (pre- or post-administration, if applicable), severity grading and study group (Table 174 through Table 176 for **Part A** and Table 177 **-** Table 178 for **Part B**, **Appendix 1**). Box plots for each parameter will be included in Figure 103 through Figure 106 for **Part A** and Figure 107 through Figure 110 for **Part B** (**Appendix 2**).

9. IMMUNOGENICITY EVALUATION

The principal immunogenicity endpoints are measured at Day 0 (Visit 02) and 4 weeks after the third administration (Visit 05) by NAb. We assume NAb results will follow a log-normal distribution.

The following summaries will be presented by study group and study visit separately for Part A and Part B for all subjects in each of the ITT, PP and mITT analysis populations. Summaries are presented over all subjects and stratified by baseline ZIKV serostatus.

- The number and percentage of subjects with positive NAb response, defined as a titer≥30, along with their exact 95% CIs and p-values from a Chi-squared test comparing study groups. (Table 19 through Table 24**, Appendix 1**)
- GMTs and their CIs, p-values from a t-test comparing log-NAb titers between study groups. (Table 25 through Table 30**, Appendix 1**)
- Geometric mean fold rise (GMFR) in NAb from baseline with the corresponding confidence interval and (1) p-value from a paired t-test comparing the log-NAb titers between baseline and post-administration within each treatment arm, and (2) p-value from t-test comparing log-transformed fold increases in NAb between study groups. Non-parametric tests will be considered if the normality assumption is not realized. (Table 25 through Table 30, **Appendix 1**)
- Boxplots of NAb titers. (Figure 15 through Figure 26**, Appendix 2**)
- Reverse cumulative distribution curves of NAb titers. (Figure 3 through Figure 14**, Appendix 2**)

Exploratory analysis of NAb for other visits will be presented in a similar fashion as data are available.

A listing of individual NAb titer levels, whether positive and the corresponding planned and actual collection dates are presented in Listing 16 **-** Listing 17, **Appendix 3.** For any immunogenicity reports released prior to database lock and study unblinding, a coded subject identifier will be included in listings to prevent unblinding any subject's study product assignment.

10. EFFICACY ANALYSIS

As one of the primary and secondary objectives of **Part B**, an efficacy evaluation with respect to ZIKV incidence will be performed. Tables providing efficacy data analysis (Table 45 through Table 56, **Appendix 1**) may be excluded if there are only a nominal number of Zika cases.

For primary analysis:

- **Case of ZIKV infection**: Virologically confirmed infection by PCR or other virus detection method in blood or in urine.

The final efficacy analysis will occur when the total of 90 ZIKV cases have been reported in the mITT population or following database lock and receipt of PCR or other virus detection assay results. If additional cases are reported following the data cut-off for this analysis and before the database lock, this analysis will be repeated and will include all cases reported during the study for inclusion in the final analyses.

For secondary analysis:

- **Subclinical case of ZIKV infection:** PCR virus detection in blood or in urine with *no* signs or symptoms. Subclinical cases of ZIKV infection will be identified by retrospective PCR or other virus testing methods.

For exploratory analysis:

- **Symptomatic case of ZIKV infection:** PCR or other virus detection method in blood or in urine in conjunction with at least one clinical sign and/or symptom.

The analyses requiring retrospective assessment of stored samples, will be conducted after database lock and Zika results are available for all subjects for inclusion in the final analysis.

For all subjects with suspected ZIKV infection a listing of all signs/and symptoms, PCR or other Zika results, and for confirmed cases, neurological symptoms, severity, and outcome are included in Listing 20 - Listing 21 for **Part B, Appendix 3.** Of note, Listing 18 - Listing 19 will include ZIKV data collected in **Part A**, which does not contribute to the efficacy analysis.

10.1. Analysis of ZIKV Incidence

For Part B, incidence will be summarized for each ZIKV endpoint as the number and percentage of subjects along with 95% CI and be described by study group, and stratified by baseline ZIKV seroprevalence. Incidence summaries will be presented for the ITT, mITT, and PP populations, Table 45 through Table 47**, Appendix 1.** Incidence for each ZIKV endpoint will also be summarized in a similar presentation by clinical site Table 48 through Table 50**, Appendix 1**.

10.2. Analysis of vaccine efficacy:

The time of ZIKV events is defined as the illness onset date recorded on the ZIKV Endpoints eCRF (for clinical cases) or date first specimen was collected with a positive PCR or other Zika result, whichever is earliest. Time to event for analysis will be as follows:

- For subjects with infection: time of ZIKV event minus date of first administration (Visit 02) + 1.
- For subjects with no infection: date of protocol completion/termination as recorded on the study status eCRF minus date of first administration (Visit 02) + 1. These subjects will be censored at their date of study completion or date of early termination.
- Subjects with or without infection may be censored from the analysis for the PP population as described in Section 6.3.

For subjects who were randomized but did not receive any product, date of randomization will be used in place of date of first administration in the definitions above.

The cumulative incidence of ZIKV cases will be presented graphically as 1 – Kaplan-Meier curves. Curves will be presented by study group and baseline ZIKV stratum and by study group combined over all subjects (Figure 27 through Figure 44**, Appendix 2**). Similar presentations will be displayed for virologic ZIKV cases and subclinical ZIKV cases).

Vaccine efficacy will be estimated as 1 - Hazard Ratio estimated from a Cox proportional hazard model. The primary efficacy analysis for ZIKV infection will use the following test:

H_0: VE $\leq$ 20%
H_1: VE >20%

The criterion for success will be that a one-sided test of H_0 has p-value $\leq$0.025. Success will be met if the lower bound of the 95.0% confidence interval for VE estimated for the mITT population using a Cox proportional hazards model stratified by baseline ZIKV status is >20 (Table 51 through Table 53**, Appendix 1**).

If the null hypothesis VE $\leq$20% is not rejected, then the following will be tested using a one-sided type I error rate of 0.025.

H^*_0: VE =0%
H^*_1: VE >0%

As secondary analyses of vaccine efficacy this hypothesis will be tested for:

- ZIKV cases without stratification for baseline ZIKV serostatus
- virologic ZIKV cases stratified by baseline ZIKV serostatus
- subclinical ZIKV cases stratified by baseline ZIKV serostatus
- subclinical ZIKV cases without stratification for baseline ZIKV serostatus

All analyses will be included in Table 51 through Table 53**, Appendix 1**. All efficacy analyses will be conducted for ITT, mITT, and PP populations. For all analyses the assumptions of proportional hazards and non-informative censoring will be evaluated.

10.2.1. Sample SAS code for time to event analysis:

Notations

Timevar = the variable that gives the time to occurrence
Censorvar = the variable indicating whether timevar is censored, where 1 = censored, 0 = not censored (event)
Trtmnt = study product (placebo or ZIKVwt DNA)
Stratavar = variable indicating baseline ZIKV serostatus

Cox Proportional Hazard

SAS Code for stratified Cox Regression [4] to obtain Vaccine Efficacy and 95% CI for Vaccine Efficacy:

```
Proc phreg;
      CLASS trtmnt (ref = 'placebo') / param = ref;
      STRATA stratavar;
      MODEL timevar*censorvar(1)=trtmnt (and any covariates)/rl;
      ODS OUTPUT ParameterEstimates=ests (keep=HazardRatio HRUpperCL
      HRLowerCL);
      RUN;
```

Calculate the following from the estimates obtained from the PROC PHREG output:

Vaccine Efficacy = 1 – HazardRatio
Lower 95% CI= 1 – HRUpperCL
Upper 95% CI= 1 – HRLowerCL

Similar code will be used to fit the cox regression combined across ZIKV serostatus stratum by removing the STRATA statement on PROC PHREG.

10.3. Analysis of Clinical Signs and Symptoms of ZIKV Illness

For confirmed ZIKV cases (primary endpoint), the number and percentage of subjects reporting each sign/symptom collected on the ZIKV Endpoint eCRF will be presented by study group in Table 51 through Table 53**, Appendix 1**. Continuous summary statistics for the duration of ZIKV illness, defined as date of resolution or death minus illness onset date plus 1 will be shown in Table 57 through Table 59**, Appendix 1**.

11. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as "> 0.999". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages, including VE, will be reported to the nearest tenth. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

12. TECHNICAL DETAILS

SAS version 9.3 or above will be used to generate all tables, figures and listings.

13. REFERENCES

1. Fauci, A.S. and D.M. Morens, Zika Virus in the Americas--Yet Another Arbovirus Threat. N Engl J Med, 2016. 374(7): p. 601-4.
2. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome. 2016.
3. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.
4. Allison, P. Survival Analysis Using SAS. 2010

14. LISTING OF TABLES, FIGURES AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3, respectively.

APPENDIX 1: TABLES

Table 1: Summary of Screen Failures, All Enrolled Subjects

	All Subjects (N = XX)	
Reason for Screen Failure[1]	n	%
Not Eligible	x	x.x
Laboratory finding(s)	x	x.x
Physical exam finding(s)	x	x.x
Medical history	x	x.x
Other	x	x.x
Eligible but not Randomized	x	x.x
Time commitment	x	x.x
Concern of potential risks	x	x.x
Number of procedures/blood draws	x	x.x
Unable to contact subject	x	x.x
Study closed out	x	x.x
Other	x	x.x

[1]Subjects may be counted under multiple criteria
N = number of subjects screened

Note, there was only a single segment of the protocol for screening subjects into both Part A and Part B

Table 2: Summary of Screen Failures by Site, All Enrolled Subjects

Reason for Screen Failure[1]	**Site 1 (N = XX)**		**Site 2 (N = XX)**		**[Repeat for all sites]**	
	n	**%**	**n**	**%**	**n**	**%**
Not Eligible						
Laboratory finding(s)						
Physical exam finding(s)						
Medical history						
Other						
Eligible but not Randomized						
Time commitment						
Concern of potential risks						

Reason for Screen Failure[1]	**Site 1 (N = XX)**		**Site 2 (N = XX)**		**[Repeat for all sites]**	
	n	**%**	**n**	**%**	**n**	**%**
Number of procedures/blood draws						
Unable to contact subject						
Study closed out						
Other						

1.Subjects may be counted under multiple criteria
N = number of subjects screened

Note, there was only a single segment of the protocol for screening subjects into both Part A and Part B

Table 3: Subject Disposition by Study Group– Part A

Subject Disposition	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%
Randomized								
Received First Administration								
Received Second Administration								
Received Third Administration								
Early Termination								
Completed Per Protocol Population[1]								
Completed mITT Population[1]								

[1] Subjects removed from the per protocol population and mITT are listed in Listing 8.
N = number of subjects randomized

Table with similar format:

Table 4: Subject Disposition by Study Group– Part B

Table 5: Subject Disposition by Site, All Enrolled Subject – Part A

Subject Disposition	Site 1 (N = XX)		Site 2 (N = XX)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	x	x.x	x	x.x	x	x.x
Randomized						
Received First Administration						
Received Second Administration						
Received Third Administration						
Early Termination						
Lost to Per Protocol Before Administration 3						

Table with similar format:

Table 6: Subject Disposition by Site, All Enrolled Subjects – Part B

Table 7: Analysis Populations by Study Group, All Randomized Subjects – Part A

Analysis Population/ Reasons for Exclusion	**Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)**		**Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)**		**Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)**		**All Subjects (N=X)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Safety Population/	x	x.x	x	x.x	x	x.x	x	x.x
No study product administered								
No post administration safety assessments								
Intent-to-treat								
Modified intent-to-treat/								
Not all 3 study product administrations received								
PCR confirmed symptomatic ZIKV infection on or before 1 week after third administration.								
Per Protocol/								
All 3 study product administrations not received								
PCR confirmed symptomatic ZIKV infection on or before 1 week after third administration.								
<Additional per protocol population exclusion categories will be defined following the examination of the protocol deviations>								
N = Number of Randomized Subjects								

Table with similar format:

Table 8: Analysis Populations by Study Group, All Randomized Subjects – Part B

Table 9: Summary of Subject-Specific Protocol Deviations by Category, Reason, and Study Group, ITT Population – Part A

Category	Reason for Deviation	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.
Eligibility	Any type								
	Subject illness	x	x	x	x	x	x	x	x
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Product administration schedule	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								

Category	Reason for Deviation	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.
	Other								
Follow-up visit schedule	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Protocol procedure/assessment	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Product administration	Any type								

Category	Reason for Deviation	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Blinding policy/procedure	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Informed consent/assent	Any type								
	Subject illness								
	Subject unable to comply								

Category	Reason for Deviation	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Study product dispensation	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Clinical endpoint	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								

Category	Reason for Deviation	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Adverse event	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								
	Laboratory error								
	Investigator/study decision								
	Other								
Serious adverse event	Any type								
	Subject illness								
	Subject unable to comply								
	Subject refusal								
	Clinic error								
	Pharmacy error								
	PharmaJet malfunction								

Category	Reason for Deviation	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.	n Subj.	n Dev.
	Laboratory error								
	Investigator/study decision								
	Other								

[Implementation note: any rows with zero deviations for the category/reason being reporting should not be displayed]

Tables with similar format:

Table 10: Summary of Subject-Specific Protocol Deviations by Category, Reason, and Study Group, ITT Population – Part B

Table 11: Summary of Subject-Specific Protocol Deviations by Category and Reason – Screening Segment

Table 12: Summary of Non-Subject Specific Protocol Deviations by Category, Reason, and Site – Parts A and B

Category	Reason for Deviation	Number of Deviations			
		[Site 1]	[Site 2]	[Site 3]	All Sites
Eligibility	Any type	x	x	x	x
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				

Category	Reason for Deviation	Number of Deviations			
		[Site 1]	[Site 2]	[Site 3]	All Sites
	Other				
Product administration schedule	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Follow-up visit schedule	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Protocol procedure/assessment	Any type				
	Subject illness				
	Subject unable to comply				

Category	Reason for Deviation	Number of Deviations			
		[Site 1]	[Site 2]	[Site 3]	All Sites
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Product administration	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Blinding policy/procedure	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				

Category	Reason for Deviation	Number of Deviations			
		[Site 1]	[Site 2]	[Site 3]	All Sites
	Laboratory error				
	Investigator/study decision				
	Other				
Informed consent/assent	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Study product dispensation	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Clinical endpoint	Any type				

Category	Reason for Deviation	Number of Deviations			
		[Site 1]	[Site 2]	[Site 3]	All Sites
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Adverse event	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				
Serious adverse event	Any type				
	Subject illness				
	Subject unable to comply				
	Subject refusal				
	Clinic error				

Category	Reason for Deviation	Number of Deviations			
		[Site 1]	[Site 2]	[Site 3]	All Sites
	Pharmacy error				
	PharmaJet malfunction				
	Laboratory error				
	Investigator/study decision				
	Other				

Table 13: Summary of Demographic Characteristics, by Study Group, ITT population– Part A

Category	Characteristic	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
GENDER	Male								
	Female								
	Unknown or Not Reported								
AGE	18-20								
	21-30								
	31-35								
	Mean (S.D.)								
	Range								
ETHNICITY	Hispanic/Latino								
	Non-Hispanic/Latino								
	Unknown or Not Reported								
RACE	White								

Category	Characteristic	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
	Black or African American								
	American Indian or Alaska Native								
	Asian								
	Native Hawaiian or Other Pacific Islander								
	Multiracial								
	Unknown or Not Reported								
LANGUAGE	English								
	French								
	Spanish								
	Portuguese								
	Creole								
	German								
	Polish								
	Other								
WEIGHT (kg)	Mean (S.D.)								
	Range								

Tables with similar format: Part B tables should include an additional Age category of 15-18

Table 19: Summary of Pre-Existing Medical Conditions by MedDRA® System Organ Class and Study Group, ITT Population – Part A

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		All Subjects (N=X)	
MedDRA® System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]								
[SOC 2]								

Note: A subject is only counted once per SOC.

Table with similar format

Table 20: Summary of Pre-Existing Medical Conditions by MedDRA® System Organ Class and Study Group, ITT Population – Part B

Table 21: Summary of Subjects with Positive Response to ZIKV Neutralizing Antibody (EC_{50}) by Study Visit, Study Group and Baseline Zika Serostatus, ITT Population – Part A

Study Visit	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)				Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)				Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)				Chi-Square test p-value		
	N meas.	N resp	%	95% CI	N meas.	N resp	%	95% CI	N meas.	N resp	%	95% CI	Group 1 vs Group 2	Group 2 vs Group 3	Group 1 vs Group 3
All Subjects															
Baseline, Pre-administration	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.xxx	x.xxx	x.xxx
Visit 05, 4 weeks post 3rd administration	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.xxx	x.xxx	x.xxx
Baseline Zika Negative															
Baseline, Pre-administration	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.xxx	x.xxx	x.xxx
Visit 05, 4 weeks post 3rd administration	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.xxx	x.xxx	x.xxx
Baseline Zika Positive															
Baseline, Pre-administration	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.xxx	x.xxx	x.xxx
Visit 05, 4 weeks post 3rd administration	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.xxx	x.xxx	x.xxx

N meas = number of subjects with Neutralizing Antibody data reported. N resp = number of responders. Positive response is defined as a titer >30.
95% CIs calculated using Clopper-Pearson exact methodology.

[Implementation note: Additional visits may be added to this table if NAb data are available for exploratory time points. For Part B tables include a Chi-square test comparing Group 4 and Group 5]

Tables with similar format:

Table 33: Geometric Mean Titers of ZIKV Neutralizing Antibody (EC_{50}) by Study Visit, Study Group and Baseline Zika Serostatus, ITT Population – Part A

Study Visit	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)			Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)			Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)			t- test p-value		
	N meas.	GMT	95% CI	N meas.	GMT	95% CI	N meas.	GMT	95% CI	Group 1 vs Group 2	Group 2 vs Group 3	Group 1 vs Group 3
All Subjects												
Baseline, Pre-administration	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Visit 05, 4 weeks post 3rd administration	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Geometric Mean Fold Rise (Visit 05)	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	-	-	-
Baseline Zika Negative												
Baseline, Pre-administration	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
4 weeks post 3rd administration	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Geometric Mean Fold Rise (Visit 05)	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	-	-	-
Baseline Zika Positive												
Baseline, Pre-administration	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
4 weeks post 3rd administration	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Geometric Mean Fold Rise (Visit 05)	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	-	-	-

N meas = number of subjects with Neutralizing Antibody data reported. For geometric mean fold-rise only subjects with baseline and post-administration are included.

Table 45: Incidence of ZIKV Cases by Serostatus and Study Group, ITT Population - Part B

ZIKV Case Definition	Baseline Serostatus	[Group 4] (N=X)			[Group 5] (N=X)			Overall (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Virologic ZIKV Case	Overall	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	ZIKV Positive	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	ZIKV Negative	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Subclinical ZIKV Case	Overall									
	ZIKV Positive									
	ZIKV Negative									
Symptomatic ZIKV Case	Overall									
	ZIKV Positive									
	ZIKV Negative									

Tables with similar formats:

Table 46: Incidence of ZIKV Cases by Serostatus and Study Group, mITT Population - Part B

Table 47: Incidence of ZIKV Cases by Serostatus and Study Group, PP Population - Part B

Table 48: Incidence of ZIKV Cases by Site and Study Group, ITT Population – Part B

ZIKV Case Definition	Site	[Group 4] (N=X)			[Group 5] (N=X)			Overall (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Virologic ZIKV Case	[Site 1]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	[Site 2]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	[Repeat for all sites]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Subclinical ZIKV Case	[Site 1]									
	[Site 2]									
	[Repeat for all sites]									
Symptomatic ZIKV Case	[Site 1]									
	[Site 2]									
	[Repeat for all sites]									

Tables with similar formats:

Table 49: Incidence of ZIKV Cases by Site and Study Group, mITT Population – Part B

Table 50: Incidence of ZIKV Cases by Site and Study Group, PP Population – Part B

Table 51: Number and Percentage of Subjects Reporting ZIKV Signs/Symptoms by Study Group, ITT Population – Part B

Zika Signs/Symptoms	[Group 4] (N=X)		[Group 5] (N=X)		Overall (N=X)	
	n	%	n	%	n	%
Fever						
Rash						
Conjunctivitis						
Arthralgia						
Headache						
Myalgia						
Peripheral edema						
Retro-orbital pain						
Sore throat						
Vomiting/Nausea						
Malaise/Fatigue						
Guillain-Barre Syndrome						
Meningitis						
Encephalitis						
Meningoencephalitis						
Other						

Tables with similar format:

Table 52: Number and Percentage of Subjects Reporting ZIKV Signs/Symptoms by Study Group, mITT Population – Part B

Table 53: Number and Percentage of Subjects Reporting ZIKV Signs/Symptoms by Study Group, PP Population – Part B

Table 54: Vaccine Efficacy for Time to Occurrence of ZIKV Cases by Serostatus and Study Group, ITT Population - Part B

ZIKV Case Definition	Baseline Serostatus	[Group 4]	[Group 5]	Vaccine Efficacy		
		N	N	%	95% CI	p-value
Virologic ZIKV Case	Overall	x	x	x	x.x, x.x	x.xxx
	ZIKV Positive	x	x	x	x.x, x.x	x.xxx
	ZIKV Negative	x	x	x	x.x, x.x	x.xxx
Subclinical ZIKV Case	Overall					
	ZIKV Positive					
	ZIKV Negative					
Symptomatic ZIKV Case	Overall					
	ZIKV Positive					
	ZIKV Negative					

Vaccine efficacy obtained from Cox Proportional Hazard model
95% CI = 95% confidence interval obtained from Cox Proportional Hazard model
p-value = result of comparison of Kaplan-Meier survival curves between groups by Log-rank test

Tables with similar format:

Table 55: Vaccine Efficacy for Time to Occurrence of ZIKV Cases by Serostatus and Study Group, mITT Population - Part B

Table 56: Vaccine Efficacy for Time to Occurrence of ZIKV Cases by Serostatus and Study Group, PP Population - Part B

Table 57: Duration of ZIKV Illness, ITT Population - Part B

	Statistic	[Group 4] (N=X)	[Group 5] (N=X)	Overall (N=X)
Duration of ZIKV Illness	N	x		
	Mean	xx.x		
	Standard Deviation	xx.x		
	Median	xx.x		
	Min, Max	xx.x, xx.x		

Tables with similar format:

Table 58: Duration of ZIKV Illness, mITT Population - Part B

Table 59: Duration of ZIKV Illness, PP Population - Part B

Table 60: Number and Percentage of Subjects Experiencing Solicited Events, Safety Analysis Population – Part A

Symptom	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)				Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)				Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)				Chi-Square test p-value		
	N meas.	N resp	%	95% CI	N meas.	N resp	%	95% CI	N meas.	N resp	%	95% CI	Group 1 vs Group 2	Group 2 vs Group 3	Group 1 vs Group 3
Any Symptom	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.xxx	x.xxx	x.xxx
Any Systemic Symptom	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.xxx	x.xxx	x.xxx
Malaise															
Myalgia															
Headache															
Chills															
Nausea															
Joint Pain															
Temperature															
Any Local Symptom															
Pain/Tenderness															
Swelling															
Redness															

Note: Subjects are counted at most once for each symptom considering solicited symptoms reported after any an administration
N. meas = the number of subjects with non-missing data for at least one post-administration assessment for the symptom being summarized.

Table with similar format:

Table 61: Number and Percentage of Subjects Experiencing Solicited Events, Safety Analysis Population – Part B

Table 62: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Administration, and Study Group, Safety Analysis Population – Part A

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)				Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)				Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)				
Symptoms Intensity	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Overall Incidence (N=X)**
PAIN/TENDERNESS													
None	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%)
Mild													
Moderate													
Severe													
Missing													
SWELLING													
None													
Mild													
Moderate													
Severe													
Missing													
REDNESS													
None													
Mild													
Moderate													
Severe													
Missing													
ANY LOCAL SYMPTOM													

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)				Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)				Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)				
Symptoms Intensity	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Overall Incidence (N=X)**
None													
Mild													
Moderate													
Severe													
Missing													
MALAISE													
None													
Mild													
Moderate													
Severe													
Missing													
MYALGIA													
None													
Mild													
Moderate													
Severe													
Missing													
HEADACHE													
None													
Mild													
Moderate													
Severe													

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)				Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)				Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)				
Symptoms Intensity	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Overall Incidence (N=X)**
Missing													
CHILLS													
None													
Mild													
Moderate													
Severe													
Missing													
NAUSEA													
None													
Mild													
Moderate													
Severe													
Missing													
JOINT PAIN													
None													
Mild													
Moderate													
Severe													
Missing													
TEMPERATURE													
None													
Mild													

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)				Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)				Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)				
Symptoms Intensity	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Admin 1 (N=X)**	**Admin 2 (N=X)**	**Admin 3 (N=X)**	**Overall (N=X)**	**Overall Incidence (N=X)**
Moderate													
Severe													
Missing													
ANY SYSTEMIC SYMPTOM													
None													
Mild													
Moderate													
Severe													
Missing													

Severity is the maximum severity reported post dosing for each subject.

Table with similar format:

Table 63: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Administration, and Study Group, Safety Analysis Population – Part B

Table 64: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class and Preferred Term, and Study Group, Safety Analysis Population Post Any Administration– Part A

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)			Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)			Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)			Fisher's Exact p-value		
SYSTEM ORGAN CLASS/ Preferred Term	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**Group 1 vs Group 2**	**Group 2 vs Group 3**	**Group 1 vs Group 3**
SYSTEM ORGAN CLASS #1	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Preferred Term #1	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Preferred Term #2	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
SYSTEM ORGAN CLASS #2	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Preferred Term #1	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Preferred Term #2	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
SYSTEM ORGAN CLASS #3	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Preferred Term #1	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx
Preferred Term #2	x	x	x.x-x.x	x	x	x.x-x.x	x	x	x.x-x.x	x.xxx	x.xxx	x.xxx

Note: A subject is counted at most once per SOC and PT

N = the number of subjects in the Safety analysis population who received the applicable dose.

[Implementation note: Table for Part A should use Fisher's exact test for calculating p-values. Tables for Part B should use Chi-square test for calculating p-values.]

Table 65: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class and Preferred Term, and Study Group, Safety Analysis Population Post First Administration– Part A

[Implementation note: Table will only include unsolicited adverse events occurring after the first administration but before the second administration.]

MedDRA® System Organ Class	MedDRA® Preferred Term	Post Dose 1 Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)			Post Dose 1 Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)			Post Dose 1 Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any SOC	Any PT	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
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: This table presents number and percentage of subjects. A subject is only counted once per PT/time point.

MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity						Relationship to Treatment			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: This table presents number and percentage of subjects. A subject is only counted once per PT and is summarized according to their highest severity and closest relationship.

Tables with similar format:

Table 74: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, Relationship, and Study Group – Part A, Group 2 (N=X)

Table 75: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, Relationship, and Study Group – Part A, Group 3 (N=X)

Table 76: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, Relationship, and Study Group – Part B, Group 4 (N=X)

				Severity						Relationship to Treatment			
		Any Incidence		Mild		Moderate		Severe		Not Related		Related	
MedDRA® System Organ Class	MedDRA® Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Tables with similar format:

Table 77: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, Relationship, and Study Group – Part B, Group 5 (N=X)

Table 78: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, Relationship, and Study Group – Screening Segment (N=X)

Table 79: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, and Study Group – Part A, Group 1 (N=X)

				Severity					
		Any Incidence		Mild		Moderate		Severe	
MedDRA® System Organ Class	MedDRA® Preferred Term	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT								
	[PT 1]								
	[PT 2]								
[SOC 2]	Any PT								
	[PT 1]								
	[PT 2]								

Note: This table presents number and percentage of subjects. A subject is only counted once per PT and is summarized according to their highest severity.

Tables with a similar format:

Table 80: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, and Study Group – Part A, Group 2 (N=X)

Table 81: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, and Study Group – Part A, Group 3 (N=X)

Table 82: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, and Study Group – Part B, Group 4 (N=X)

				Severity					
		Any Incidence		Mild		Moderate		Severe	
MedDRA® System Organ Class	MedDRA® Preferred Term	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT								
	[PT 1]								
	[PT 2]								
[SOC 2]	Any PT								
	[PT 1]								
	[PT 2]								

Note: This table presents number and percentage of subjects. A subject is only counted once per PT and is summarized according to their highest severity

Tables with similar format:

Table 83: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, and Study Group – Part B, Group 5 (N=X)

Table 84: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Severity, and Study Group – Screening Segment (N=X)

Table 85: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Post Dosing by MedDRA® System Organ Class and Preferred Term, Dose, and Study Group – Part A, Group 1

		Post Dose 1 (N=X)		Post Dose 2 (N=X)		Post Dose 3 (N=X)		Post Any Dose (N=X)	
MedDRA® System Organ Class	**MedDRA® Preferred Term**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT								
	[PT 1]								
	[PT 2]								
[SOC 2]	Any PT								
	[PT 1]								
	[PT 2]								

Note: This table presents number and percentage of subjects. A subject is only counted once per PT/Time point.

Tables with similar format:

Table 86: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Post Dosing by MedDRA® System Organ Class and Preferred Term, Dose, and Study Group – Part A, Group 2

Table 87: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Post Dosing by MedDRA® System Organ Class and Preferred Term, Dose, and Study Group – Part A, Group 3

Table 88: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Post Dosing by MedDRA® System Organ Class and Preferred Term, Dose, and Study Group – Part B, Group 4

Table 89: Number and Percentage of Subjects Experiencing Related Unsolicited Adverse Events Post Dosing by MedDRA® System Organ Class and Preferred Term, Dose, and Study Group – Part B, Group 5

Table 90: Number of Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Dose, and Study Group – Part A, Group 1

[Implementation Note: Day x-y interval should correspond to period of collection for solicited symptoms, if applicable. Day y-z interval should be up until subsequent dose.]

		Post Dose 1 (N=X)	Post Dose 2 (N=X)	Post Dose 3 (N=X)	Post Any Dose (N=X)
MedDRA® System Organ Class	**MedDRA® Preferred Term**	**# of Events**	**# of Events**	**# of Events**	**# of Events**
Any SOC	Any PT	x	x	x	x
[SOC 1]	Any PT				
	[PT 1]				
	[PT 2]				
[SOC 2]	Any PT				
	[PT 1]				
	[PT 2]				

Note: This table presents number of events.

Table with similar format:

Table 95: Number and Percentage of Subjects Experiencing Adverse Events Above 5% Frequency Threshold by MedDRA System Organ Class, Preferred Term, and Study Group – Part A

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)	
	n	%	n	%	n	%
At least one solicited or unsolicited adverse event above 5%						
[SOC 1]						
[PT 1]						
[PT 2]						
[SOC 1]						

Table with similar format:

Table 96: Number and Percentage of Subjects Experiencing Adverse Events Above 5% Frequency Threshold by MedDRA System Organ Class, Preferred Term, and Study Group – Part B

Table 97: Overall Summary of Adverse Events

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		[Group 4] (N=X)		[Group 5] (N=X)		All Part A Subjects (N=X)		All Part B Subjects (N=X)		All Randomized Subjects (N=X)		Subjects in Screening
Subjects[a] with	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
At least one local solicited reactogenicity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
At least one systemic solicited reactogenicity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
At least one unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Not yet assessed																	
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Related	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one serious adverse event[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
At least one new onset chronic medical condition	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		[Group 4] (N=X)		[Group 5] (N=X)		All Part A Subjects (N=X)		All Part B Subjects (N=X)		All Randomized Subjects (N=X)		Subjects in Screening
Subjects[a] with	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
N = Number of subjects in the Safety Population [a] Subjects are counted once for each category regardless of the number of events. [b] A listing of Serious Adverse Events is included in Table 99 through Table 101. [c] As reported on the Adverse Event eCRF.																	

Table 98: Number and Percentage of Subjects Experiencing Serious Adverse Events by MedDRA System Organ Class, Preferred Term, and Study Group

SYSTEM ORGAN CLASS/ Preferred Term	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)		Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)		Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)		[Group 4] (N=X)		[Group 5] (N=X)		All Randomized Subjects (N=X)		Subjects in Screening
	n	%	n	%	n	%	n	%	n	%	n	%	n
SYSTEM ORGAN CLASS #1	x	x	x	x	x	x	x	x	x	x	x	x	x
Preferred Term #1	x	x	x	x	x	x	x	x	x	x	x	x	x
Preferred Term #2	x	x	x	x	x	x	x	x	x	x	x	x	x
SYSTEM ORGAN CLASS #2	x	x	x	x	x	x	x	x	x	x	x	x	x
Preferred Term #1	x	x	x	x	x	x	x	x	x	x	x	x	x
Preferred Term #2	x	x	x	x	x	x	x	x	x	x	x	x	x
SYSTEM ORGAN CLASS #3	x	x	x	x	x	x	x	x	x	x	x	x	x
Preferred Term #1	x	x	x	x	x	x	x	x	x	x	x	x	x
Preferred Term #2	x	x	x	x	x	x	x	x	x	x	x	x	x
Note: A subject is counted at most once per SOC and PT N = the number of subjects in the Safety analysis population													

Table 99: Listing of Serious Adverse Events – Part A

1

Subject ID	Study Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	Duration (Days)	Reason Reported as an SAE	Severity

#2

Subject ID	Adverse Event	Relationship to Study Treatment	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

Table 100: Listing of Serious Adverse Events – Part B

1

Subject ID	Study Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	Duration (Days)	Reason Reported as an SAE	Severity

2

Subject ID	Adverse Event	Relationship to Study Treatment	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

Table 101: Listing of Serious Adverse Events – Screening Segment

Subject ID	Study Group	AE Number	Adverse Event	Duration (Days)	Reason Reported as an SAE	Severity	Action Taken with Study Treatment	Outcome	Comments

Table 102: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events – Part A

1

Subject ID	Study Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	Duration (Days)	Severity

#2

Subject ID	Adverse Event	Relationship to Study Treatment	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

Table 103: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events – Part B

1

Subject ID	Study Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	Duration (Days)	Reason Reported as an SAE	Severity

#2

Subject ID	Adverse Event	Relationship to Study Treatment	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

Table 104: Listing of New Onset Chronic Medical Conditions – Part A

Subject ID	Age (Years)	Study Group	AE Number	Adverse Event	Adverse Event Onset Date	Associated with Dose #	# of Days Post Associated Dose	Adverse Event End Date	Duration (Days)	Severity	Relationship to Study Treatment

Table with similar format:

Table 105: Listing of New Onset Chronic Medical Conditions – Part B

Table 106: Narratives of Deaths, Other Serious and Significant Adverse Events- All Enrolled Subjects

Table 107: Confirmed Cases of DENV, Safety Population – Part B

	[Group 4] (N=X)			[Group 5] (N=X)			Overall (N=X)			Group 4 vs Group 5 p-value
	n	%	95% CI	n	%	95% CI	n	%	95% CI	
Confirmed DENV Case	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x.xxx
Baseline Zika Negative										
Confirmed DENV Case	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x.xxx
Baseline Zika Positive										
Confirmed DENV Case	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x.xxx

Table 108: Number of Pregnancies by Outcome and Study Group – Part A

	Group 1: 4 mg ZIKVwt DNA, 2 injections (N=X)	Group 2: 4 mg ZIKVwt DNA, 4 injections (N=X)	Group 3: 8 mg ZIKVwt DNA, 4 injections (N=X)	All Subjects (N=X)
Total pregnancies	x	x	x	x
Live birth	x	x	x	x
Congenital anomalies	x	x	x	x
Neonatal deaths	x	x	x	x
Miscarriage	x	x	x	x
Elective abortion	x	x	x	x
Ectopic pregnancy	x	x	x	x
Still birth	x	x	x	x
Congenital anomalies	x	x	x	x

Table with similar format:

Table 109: Number of Pregnancies by Outcome and Study Group – Part B

Table 110: Distribution of Laboratory Results (Binary-Graded) by Parameter, Severity, Study Day, and Study Group – Part A

[For binary parameters, not contained in tox table]

		Group 1: 4 mg ZIKVwt DNA, 2 injections					Group 2: 4 mg ZIKVwt DNA, 4 injections					Group 3: 8 mg ZIKVwt DNA, 4 injections				
		N	Normal		Abnormal		N	Normal		Abnormal		N	Normal		Abnormal	
Laboratory Parameter	**Study Day**		**n**	**%**	**n**	**%**		**n**	**%**	**n**	**%**		**n**	**%**	**n**	**%**
Any Parameter	Baseline		x	x.x	x	x.x		x	x.x	x	x.x		x	x.x	x	x.x
	Day 28 (Visit 03)															
	Day 42 (Visit 03B)															
	Day 56 (Visit 04)															
	Day 70 (Visit 04B)															
	Day 84 (Visit 05)															
	Day 112 (Visit 06)															
	Max Post Baseline															
[Parameter 1]	Baseline															
	Day 28 (Visit 03)															
	Day 42 (Visit 03B)															
	Day 56 (Visit 04)															
	Day 70 (Visit 04B)															
	Day 84 (Visit 05)															
	Day 112 (Visit 06)															

Laboratory Parameter	Study Day	Group 1: 4 mg ZIKVwt DNA, 2 injections					Group 2: 4 mg ZIKVwt DNA, 4 injections					Group 3: 8 mg ZIKVwt DNA, 4 injections				
		N	Normal		Abnormal		N	Normal		Abnormal		N	Normal		Abnormal	
			n	%	n	%		n	%	n	%		n	%	n	%
	Max Post Baseline															
[Parameter 2]	Baseline															
	Day 28 (Visit 03)															
	Day 42 (Visit 03B)															
	Day 56 (Visit 04)															
	Day 70 (Visit 04B)															
	Day 84 (Visit 05)															
	Day 112 (Visit 06)															
	Max Post Baseline															

Note: The "Max Post Baseline" column includes the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table 111: Distribution of Laboratory Results (Ordinal-Graded) by Parameter, Severity, Study Day, and Study Group – Part A, Group 1

[For graded parameters, in tox table]

Laboratory Parameter	Study Day		Normal		Grade 1		Grade 2		Grade 3		Grade 4	
		N	n	%	n	%	n	%	n	%	n	%
Any Parameter	Baseline		x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Day 28 (Visit 03)											

Laboratory Parameter	Study Day		Normal		Grade 1		Grade 2		Grade 3		Grade 4	
		N	n	%	n	%	n	%	n	%	n	%
	Day 42 (Visit 03B)											
	Day 56 (Visit 04)											
	Day 70 (Visit 04B)											
	Day 84 (Visit 05)											
	Day 112 (Visit 06)											
	Max Post Baseline											
[Parameter 1]	Baseline											
	Day 28 (Visit 03)											
	Day 42 (Visit 03B)											
	Day 56 (Visit 04)											
	Day 70 (Visit 04B)											
	Day 84 (Visit 05)											
	Day 112 (Visit 06)											
	Max Post Baseline											
[Parameter 2]	Baseline											
	Day 28 (Visit 03)											
	Day 42 (Visit 03B)											
	Day 56 (Visit 04)											
	Day 70 (Visit 04B)											
	Day 84 (Visit 05)											
	Day 112 (Visit 06)											

Laboratory Parameter	Study Day	N	Normal		Grade 1		Grade 2		Grade 3		Grade 4	
			n	%	n	%	n	%	n	%	n	%
	Max Post Baseline											

Note: The "Max Post Baseline" row includes the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 112: Distribution of Laboratory Results (Ordinal-Graded) by Parameter, Severity, Study Day, and Study Group – Part A, Group 2

Table 113: Distribution of Laboratory Results (Ordinal-Graded) by Parameter, Severity, Study Day, and Study Group – Part A, Group 3

Table 114: Distribution of Laboratory Results (Binary-Graded) by Parameter, Severity, Study Day, and Study Group – Part B

Table 115: Distribution of Laboratory Results (Ordinal-Graded) by Parameter, Severity, Study Day, and Study Group – Part B, Group 4

Table 116: Distribution of Laboratory Results (Ordinal-Graded) by Parameter, Severity, Study Day, and Study Group – Part B, Group 5

Table 117: Laboratory Summary Statistics by Parameter, Study Day, and Study Group – Part A, Group 1

Laboratory Parameter	Statistic	Baseline	Day 28 (Visit 03)	Day 42 (Visit 03B)	Day 56 (Visit 04)	Day 70 (Visit 04B)	Day 84 (Visit 05)	Day 112 (Visit 06)
[Parameter 1]	N	x						
	Mean	xx.x						
	Standard Deviation	xx.x						
	Median	xx.x						

Laboratory Parameter	Statistic	Baseline	Day 28 (Visit 03)	Day 42 (Visit 03B)	Day 56 (Visit 04)	Day 70 (Visit 04B)	Day 84 (Visit 05)	Day 112 (Visit 06)
	Min, Max	xx.x, xx.x						
[Parameter 1 Change from Baseline]	N	N/A						
	Mean	N/A						
	Standard Deviation	N/A						
	Median	N/A						
	Min, Max	N/A						
[Parameter 2]	N	x						
	Mean	xx.x						
	Standard Deviation	xx.x						
	Median	xx.x						
	Min, Max	xx.x, xx.x						
[Parameter 2 Change from Baseline]	N	N/A						
	Mean	N/A						
	Standard Deviation	N/A						
	Median	N/A						
	Min, Max	N/A						

[Implementation Note: If the number of Study Groups or assessment time points causes this table to be too wide (wider than the page), then split this table by Study Group (i.e., one table per Study Group).
If there are a lot of hematology and biochemistry values, or if the time points differ for the two sets of parameters, then split this table into separate hematology and biochemistry tables. A separate table will also likely be needed for urinalysis.
Include change from baseline for each test as a Laboratory Parameter. See example below.
For calculated fields (Mean, SD, Median), decimal place should be the format in which the data were collected + 1 extra place. For Min, Max, decimal place should be in the same format in which the data were collected.]

Tables with similar format:

Table 118: Laboratory Summary Statistics by Parameter, Study Day, and Study Group – Part A, Group 2

Table 119: Laboratory Summary Statistics by Parameter, Study Day, and Study Group – Part A, Group 3

Table 120: Laboratory Summary Statistics by Parameter, Study Day, and Study Group – Part B, Group 4

[Implementation Note: If the number of Study Groups or assessment time points causes this table to be too wide (wider than the page), then split this table by Study Group (i.e., one table per Study Group).
If there are a lot of hematology and biochemistry values, or if the time points differ for the two sets of parameters, then split this table into separate hematology and biochemistry tables. A separate table will also likely be needed for urinalysis.
Include change from baseline for each test as a Laboratory Parameter. See example below.
For calculated fields (Mean, SD, Median), decimal place should be the format in which the data were collected + 1 extra place. For Min, Max, decimal place should be in the same format in which the data were collected.]

Laboratory Parameter	Statistic	Baseline	Day 28 (Visit 03)	Day 56 (Visit 04)	Day 112 (Visit 06)	Day 308 (Visit 13)
[Parameter 1]	N	x				
	Mean	xx.x				
	Standard Deviation	xx.x				
	Median	xx.x				
	Min, Max	xx.x, xx.x				
[Parameter 1 Change from Baseline]	N	N/A				
	Mean	N/A				
	Standard Deviation	N/A				
	Median	N/A				
	Min, Max	N/A				
[Parameter 2]	N	x				
	Mean	xx.x				
	Standard Deviation	xx.x				
	Median	xx.x				
	Min, Max	xx.x, xx.x				
[Parameter 2 Change from Baseline]	N	N/A				
	Mean	N/A				

	Standard Deviation	N/A				
	Median	N/A				
	Min, Max	N/A				

Table with a similar format:

Table 121: Laboratory Summary Statistics by Parameter, Study Day, and Study Group – Part B, Group 5

Table 122: Shift Table for RBC by Study Group Comparing Baseline to Post-Baseline Measures – Part A

	Group 1: 4 mg ZIKVwt DNA, 2 injections Baseline			Group 2: 4 mg ZIKVwt DNA, 4 injections Baseline			Group 3: 8 mg ZIKVwt DNA, 4 injections Baseline		
	Normal	**Abnormal**	**Total**	**Normal**	**Abnormal**	**Total**	**Normal**	**Abnormal**	**Total**
Post Baseline Week 4 (Visit 03)									
Normal									
Abnormal									
Total									
Post Baseline Week 6 (Visit 03B)									
Normal									
Abnormal									
Total									
Post Baseline Week 8 (Visit 04)									
Normal									
Abnormal									
Total									
Post Baseline Week 10 (Visit 04B)									
Normal									
Abnormal									
Total									
Post Baseline Week 12 (Visit 05)									
Normal									
Abnormal									
Total									
Post Baseline Week 16 (Visit 06)									

	Group 1: 4 mg ZIKVwt DNA, 2 injections Baseline			Group 2: 4 mg ZIKVwt DNA, 4 injections Baseline			Group 3: 8 mg ZIKVwt DNA, 4 injections Baseline		
	Normal	**Abnormal**	**Total**	**Normal**	**Abnormal**	**Total**	**Normal**	**Abnormal**	**Total**
Normal									
Abnormal									
Total									

Tables with a similar format:

Table 123: Shift Table for Hematocrit by Study Group Comparing Baseline to Post-Baseline Measures – Part A

Table 124: Shift Table for MCV by Study Group Comparing Baseline to Post-Baseline Measures – Part A

Table 125: Shift Table for Monocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part A

Table 126: Shift Table for Basophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A

Table 127: Shift Table for ALT by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

	Baseline					
	Normal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Post Baseline Week 4 (Visit 03)						
Normal	x	x	x	x	x	x
Grade 1	x	x	x	x	x	x
Grade 2	x	x	x	x	x	x
Grade 3	x	x	x	x	x	x
Grade 4	x	x	x	x	x	x
Total	x	x	x	x	x	x
Post Baseline Week 6 (Visit 03B)						
Normal	x	x	x	x	x	x
Grade 1	x	x	x	x	x	x
Grade 2	x	x	x	x	x	x
Grade 3	x	x	x	x	x	x
Grade 4	x	x	x	x	x	x
Total	x	x	x	x	x	x
Post Baseline Week 8 (Visit 04)						
Normal	x	x	x	x	x	x
Grade 1	x	x	x	x	x	x
Grade 2	x	x	x	x	x	x
Grade 3	x	x	x	x	x	x
Grade 4	x	x	x	x	x	x

	Baseline					
	Normal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Total	x	x	x	x	x	x
Post Baseline Week 10 (Visit 04B)						
Normal	x	x	x	x	x	x
Grade 1	x	x	x	x	x	x
Grade 2	x	x	x	x	x	x
Grade 3	x	x	x	x	x	x
Grade 4	x	x	x	x	x	x
Total	x	x	x	x	x	x
Post Baseline Week 12 (Visit 05)						
Normal	x	x	x	x	x	x
Grade 1	x	x	x	x	x	x
Grade 2	x	x	x	x	x	x
Grade 3	x	x	x	x	x	x
Grade 4	x	x	x	x	x	x
Total	x	x	x	x	x	x
Post Baseline Week 16 (Visit 06)						
Normal	x	x	x	x	x	x
Grade 1	x	x	x	x	x	x
Grade 2	x	x	x	x	x	x
Grade 3	x	x	x	x	x	x
Grade 4	x	x	x	x	x	x
Total	x	x	x	x	x	x

Tables with similar format:

Table 128: Shift Table for ALT by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 129: Shift Table for ALT by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 130: Shift Table for WBC by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

Table 131: Shift Table for WBC by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 132: Shift Table for WBC by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 133: Shift Table for Hemoglobin by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

Table 134: Shift Table for Hemoglobin by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 135: Shift Table for Hemoglobin by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 136: Shift Table for Platelets by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

Table 137: Shift Table for Platelets by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 138: Shift Table for Platelets by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 139: Shift Table for Neutrophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

Table 140: Shift Table for Neutrophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 141: Shift Table for Neutrophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 142: Shift Table for Lymphocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

Table 143: Shift Table for Lymphocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 144: Shift Table for Lymphocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 145: Shift Table for Eosinophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 1

Table 146: Shift Table for Eosinophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 2

Table 147: Shift Table for Eosinophils by Study Group Comparing Baseline to Post-Baseline Measures – Part A, Group 3

Table 148: Shift Table for RBC by Study Group Comparing Baseline to Post-Baseline Measures – Part B

Table 149: Shift Table for Hematocrit by Study Group Comparing Baseline to Post-Baseline Measures – Part B

Table 150: Shift Table for MCV by Study Group Comparing Baseline to Post-Baseline Measures – Part B

Table 151: Shift Table for Monocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part B

Table 152: Shift Table for Basophils by Study Group Comparing Baseline to Post-Baseline Measures – Part B

Table 153: Shift Table for ALT by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 154: Shift Table for ALT by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 155: Shift Table for WBC by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 156: Shift Table for WBC by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 157: Shift Table for Hemoglobin by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 158: Shift Table for Hemoglobin by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 159: Shift Table for Platelets by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 160: Shift Table for Platelets by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 161: Shift Table for Neutrophils by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 162: Shift Table for Neutrophils by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 163: Shift Table for Lymphocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 164: Shift Table for Lymphocytes by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 165: Shift Table for Eosinophils by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 4

Table 166: Shift Table for Eosinophils by Study Group Comparing Baseline to Post-Baseline Measures – Part B, Group 5

Table 167: Listing of Abnormal Laboratory Results- Part A

[Implementation Note: This listing is included in the table shells document, as it is included in the body of the CSR.
This listing only includes abnormal laboratory results. A complete listing of all laboratory results is included in the listings document.

In the Laboratory Parameter column, indicate the units after the parameter, e.g., Hemoglobin (g/dL).
This listing is not color-coded, but the severity should be included in parentheses after the result, e.g., 16.2 (mild).
In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon.]

Subject ID	Study Group	Sex	Age (years)	Visit Number	Date Specimen Collected	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	Action Taken with Study Treatment

Table 168: Listing of Abnormal Laboratory Results- Part B

Subject ID	Study Group	Sex	Age (years)	Visit Number	Date Specimen Collected	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	Action Taken with Study Treatment

Table 169: Distribution of Abnormal Laboratory Results (Ordinal-Graded) Related to Study Treatment by Parameter, Severity, Study Day, and Study Group – Part A, Group 1

Laboratory Parameter	Study Day		Grade 1		Grade 2		Grade 3		Grade 4	
		N	n	%	n	%	n	%	n	%
Any Parameter	Baseline		x	x.x	x	x.x	x	x.x	x	x.x
	Day 28 (Visit 03)									
	Day 42 (Visit 03B)									
	Day 56 (Visit 04)									
	Day 70 (Visit 04B)									
	Day 84 (Visit 05)									
	Day 112 (Visit 06)									
[Parameter 1]	Baseline									
	Day 28 (Visit 03)									
	Day 42 (Visit 03B)									

Laboratory Parameter	Study Day		Grade 1		Grade 2		Grade 3		Grade 4	
		N	n	%	n	%	n	%	n	%
	Day 56 (Visit 04)									
	Day 70 (Visit 04B)									
	Day 84 (Visit 05)									
	Day 112 (Visit 06)									
[Parameter 2]	Baseline									
	Day 28 (Visit 03)									
	Day 42 (Visit 03B)									
	Day 56 (Visit 04)									
	Day 70 (Visit 04B)									
	Day 84 (Visit 05)									
	Day 112 (Visit 06)									

Tables with similar formats:

Table 174: Distribution of Vital Signs by Day Post Dosing, Grade, and Study Group – Part A, Group 1

[Implementation Note: If the number of Study Groups or assessment time points causes this table to be too wide (wider than the page), then split this table by Study Group (i.e., one table per Study Group).
If an assessment has a grading scale that includes grading for both high and low, then include one row for each severity for high and low, as shown below for Assessment 1. If not, then just include one row per severity, as shown below for Assessment 2. "Any Assessment" will just summarize one row per severity.
If there are subjects with a max severity that is both high AND low for the same parameter, then break out the "Max Severity Post Baseline" columns into a separate table.]

			Normal		Mild		Moderate		Severe	
Vital Sign Assessment	**Study Day**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Assessment	Baseline		x	x.x	x	x.x	x	x.x	x	x.x
	Day 28 (Visit 03)									
	Day 42 (Visit 03B)									
	Day 56 (Visit 04)									
	Day 70 (Visit 04B)									
	Day 84 (Visit 05)									
	Day 112 (Visit 06)									
	[continue for all visits with VS]									
	Max Post Baseline									
[Assessment 1]	Baseline									
	Day 28 (Visit 03)									
	Day 42 (Visit 03B)									
	Day 56 (Visit 04)									

Vital Sign Assessment	Study Day		Normal		Mild		Moderate		Severe	
		N	n	%	n	%	n	%	n	%
	Day 70 (Visit 04B)									
	Day 84 (Visit 05)									
	Day 112 (Visit 06)									
	[continue for all visit with VS]									
	Max Post Baseline									
[Assessment 2]	Baseline									
	Day 28 (Visit 03)									
	Day 42 (Visit 03B)									
	Day 56 (Visit 04)									
	Day 70 (Visit 04B)									
	Day 84 (Visit 05)									
	Day 112 (Visit 06)									
	[continue for all visits with VS]									
	Max Post Baseline									

Table with similar format:

Table 175: Distribution of Vital Signs by Day Post Dosing, Grade, and Study Group – Part A, Group 2

Table 176: Distribution of Vital Signs by Day Post Dosing, Grade, and Study Group – Part A, Group 3

Table 177: Distribution of Vital Signs by Day Post Dosing, Grade, and Study Group – Part B, Group 4

Table 178: Distribution of Vital Signs by Day Post Dosing, Grade, and Study Group – Part B, Group 5

APPENDIX 2: FIGURES

Figure 1: CONSORT Flow Diagram – Part A

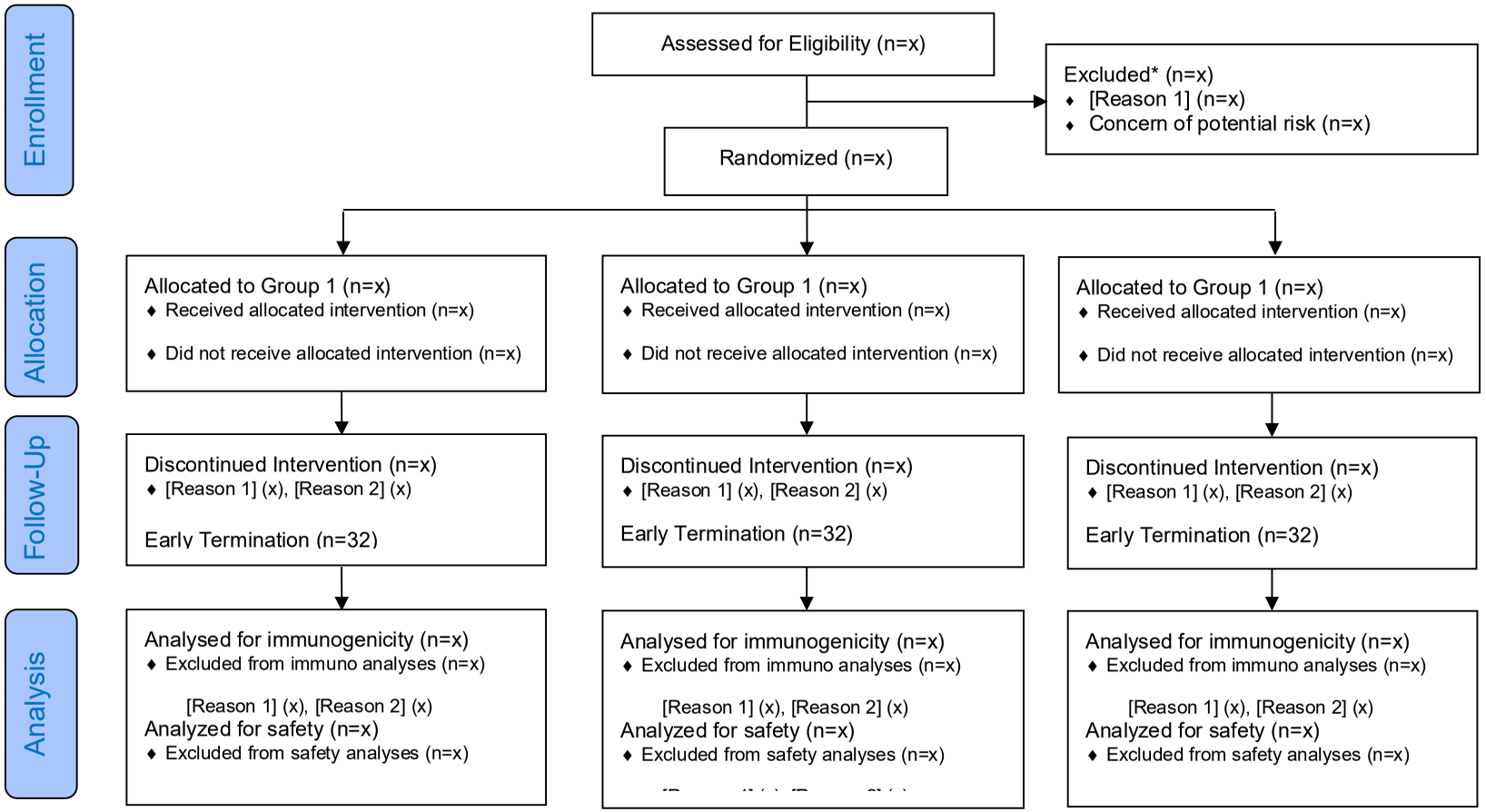
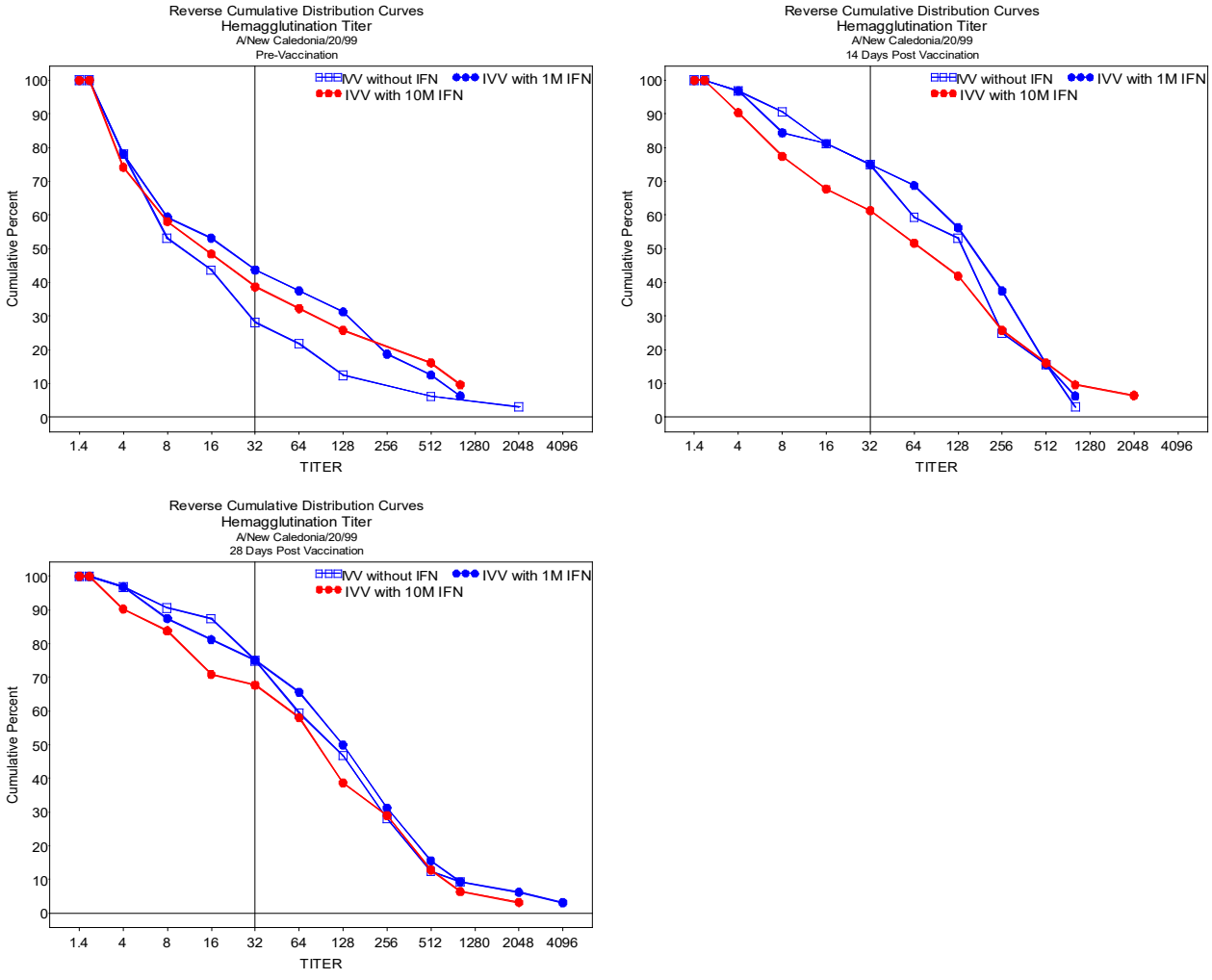


Figure with similar format:

Figure 2: CONSORT Flow Diagram – Part B

Figure 3: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, ITT Population – Part A



Figures with similar format:

Figure 4: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, mITT Population – Part A

Figure 5: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, Per Protocol Population – Part A

Figure 6: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, ITT Population – Part A

Figure 7: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, mITT Population – Part A

Figure 8: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, Per Protocol Population – Part A

Figure 9: Reverse Cumulative Distribution of Neutralizing Antibody (ID_{50}) by Time Point and Study Group, ITT Population – Part B

Figure 10: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, mITT Population – Part B

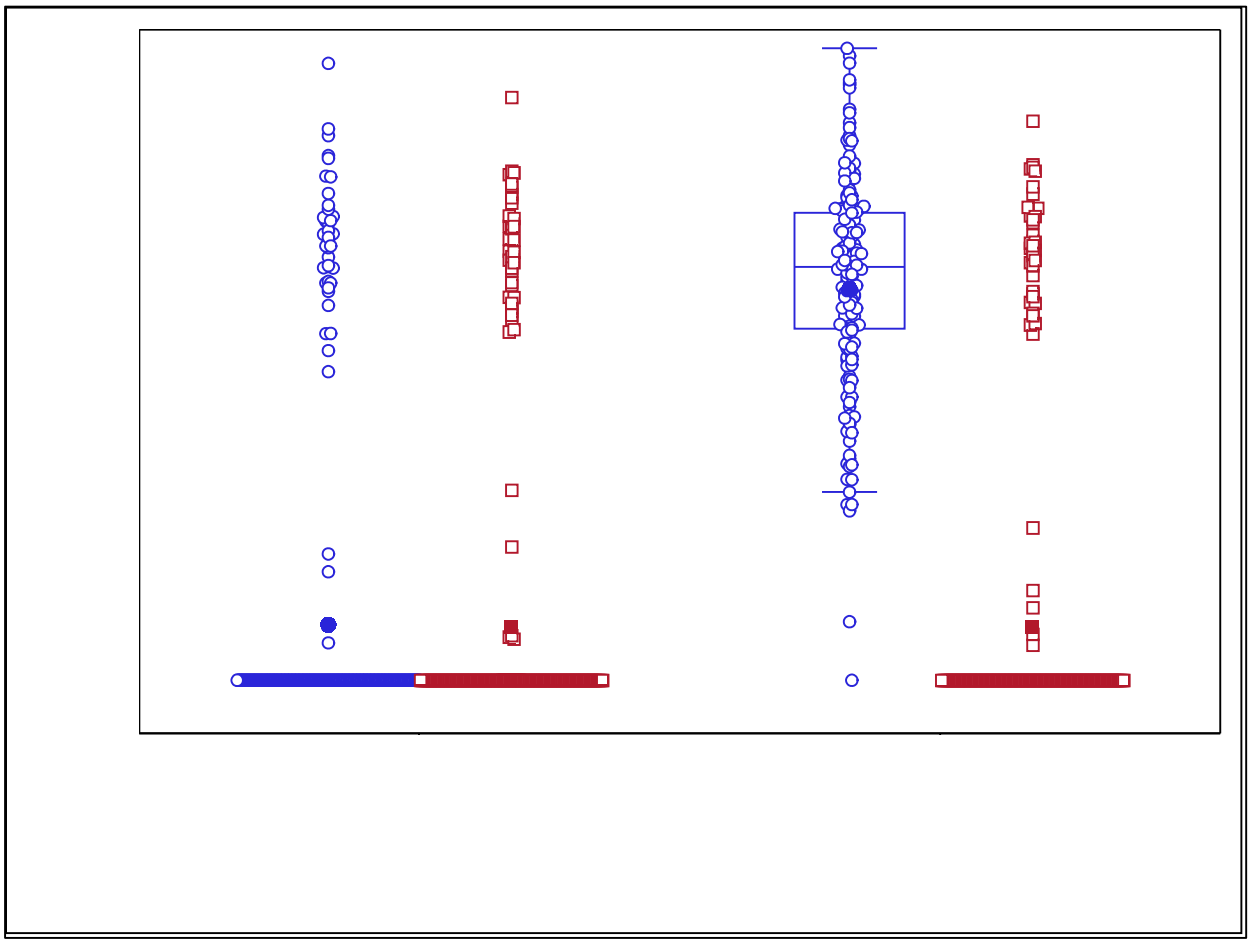
Figure 11: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, Per Protocol Population – Part B

Figure 12: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, ITT Population – Part B

Figure 13: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, mITT Population – Part B

Figure 14: Reverse Cumulative Distribution of ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, Per Protocol Population – Part B

Figure 15: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, ITT Population – Part A



Figures with similar format:

Figure 16: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, mITT Population – Part A

Figure 17: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, Per Protocol Population – Part A

Figure 18: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, ITT Population – Part A

Figure 19: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, mITT Population – Part A

Figure 20: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, Per Protocol Population – Part A

Figure 21: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID50) by Time Point and Study Group, ITT Population – Part B

Figure 22: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, mITT Population – Part B

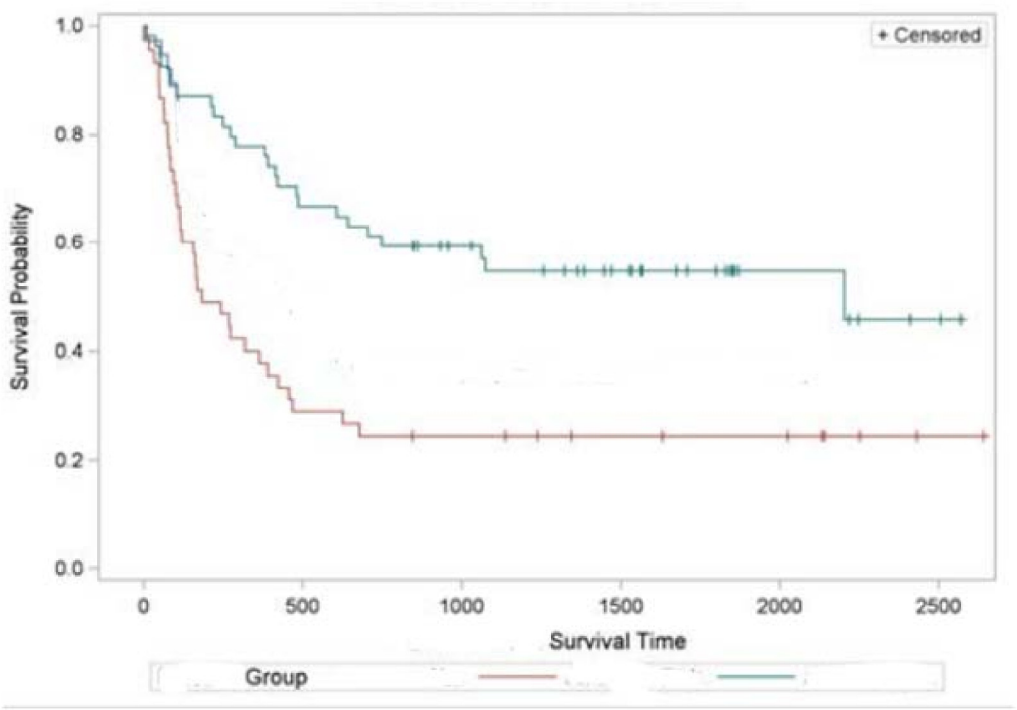
Figure 23: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{50}) by Time Point and Study Group, Per Protocol Population – Part B

Figure 24: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, ITT Population – Part B

Figure 25: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, mITT Population – Part B

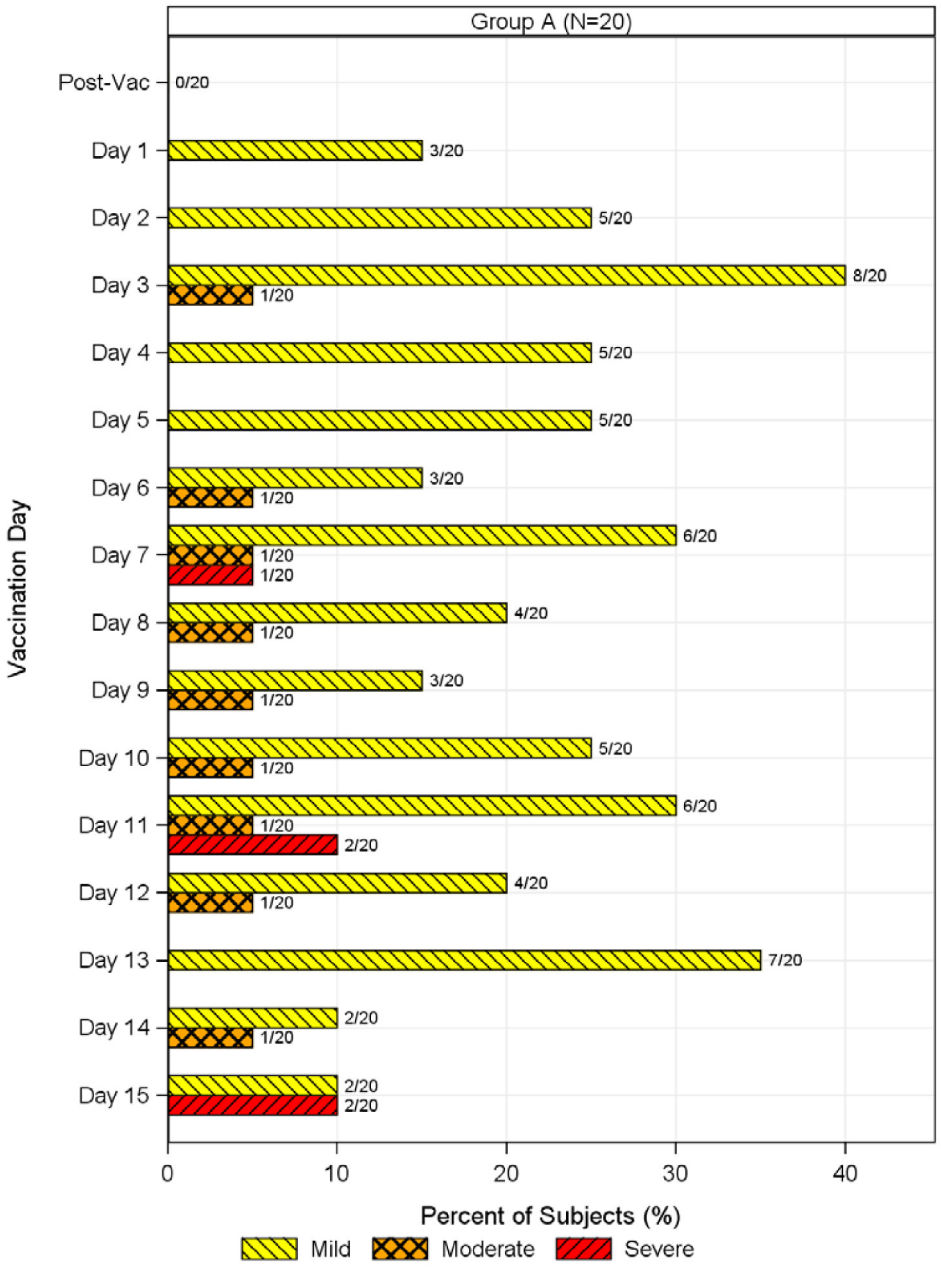
Figure 26: Boxplots with Overlaid Scatter Plots Summarizing ZIKV Neutralizing Antibody (ID_{80}) by Time Point and Study Group, Per Protocol Population – Part B

Figure 27: Kaplan-Meier Plots of Time to Infection (Virologic ZIKV cases) by Study Group, ITT population



The x-axis for the Time to Infection Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the study groups. Censored observations will be represented using a + sign. The y-axis will be labeled as Infection-free Survival.

Figures of similar format


Group A (N=20)
Post-Vac
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day 12
Day 13
Day 14
Day 15
0/20
3/20
5/20
8/20
1/20
5/20
5/20
3/20
1/20
6/20
1/20
1/20
4/20
1/20
3/20
1/20
5/20
1/20
6/20
1/20
2/20
4/20
1/20
7/20
2/20
1/20
2/20
2/20
Vaccination Day
0
10
20
30
40
Percent of Subjects (%)
Mild
Moderate
Severe

Or…

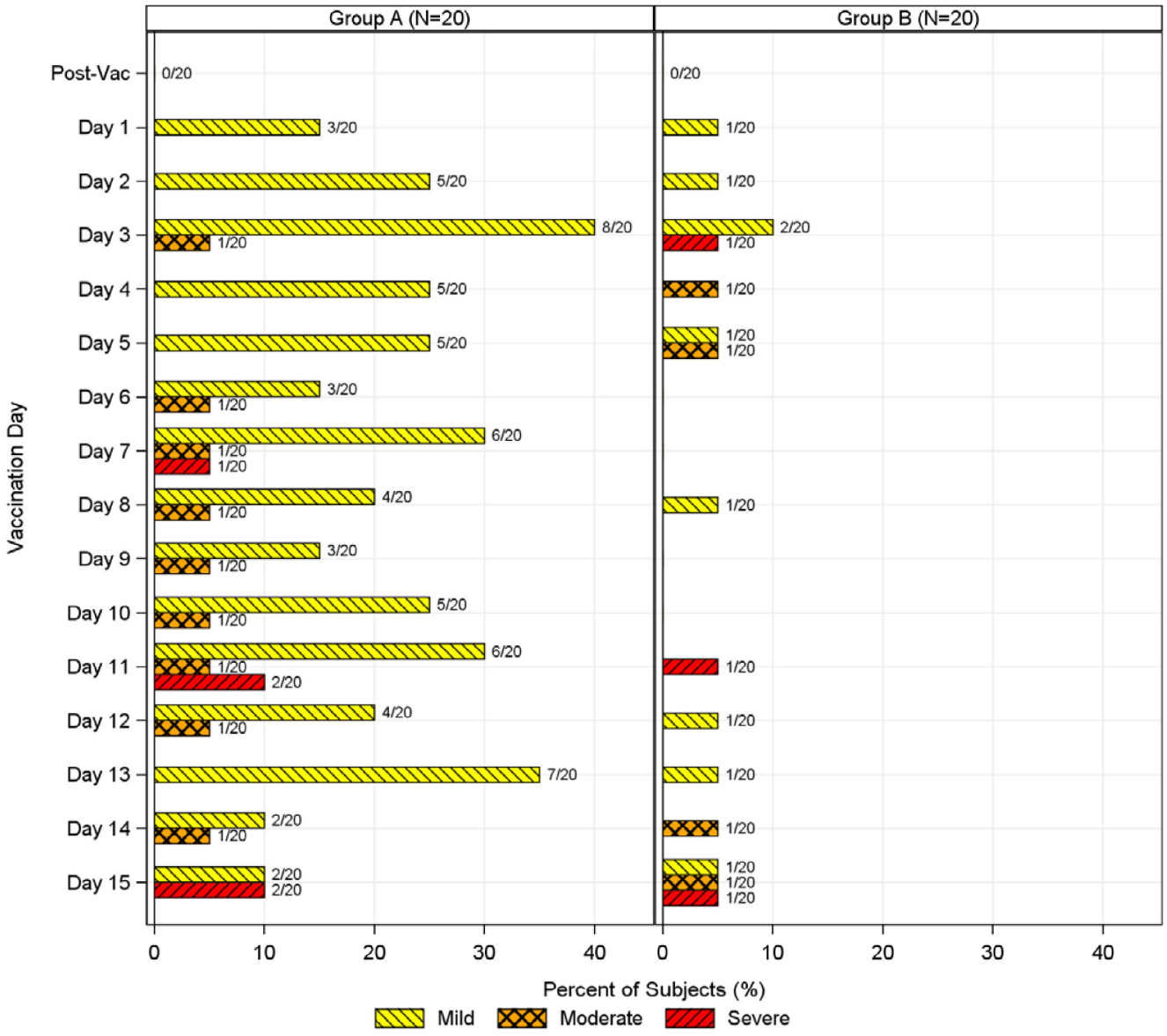
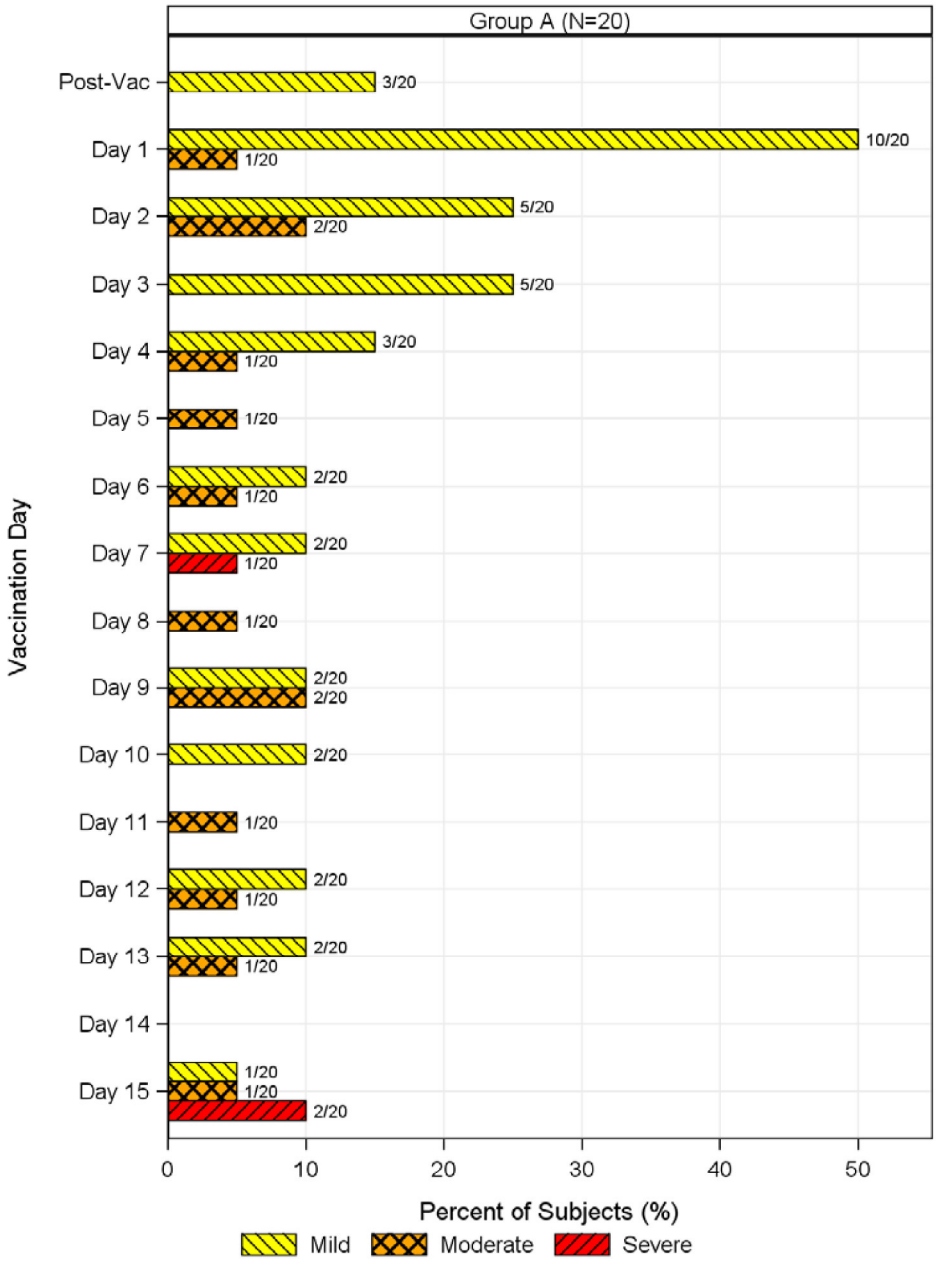


Figure with similar format:

Figure 46: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Treatment, Part B

Figure 47: Maximum Severity of Solicited Local Symptoms per Subject by Day Post Treatment, Part A



Or…

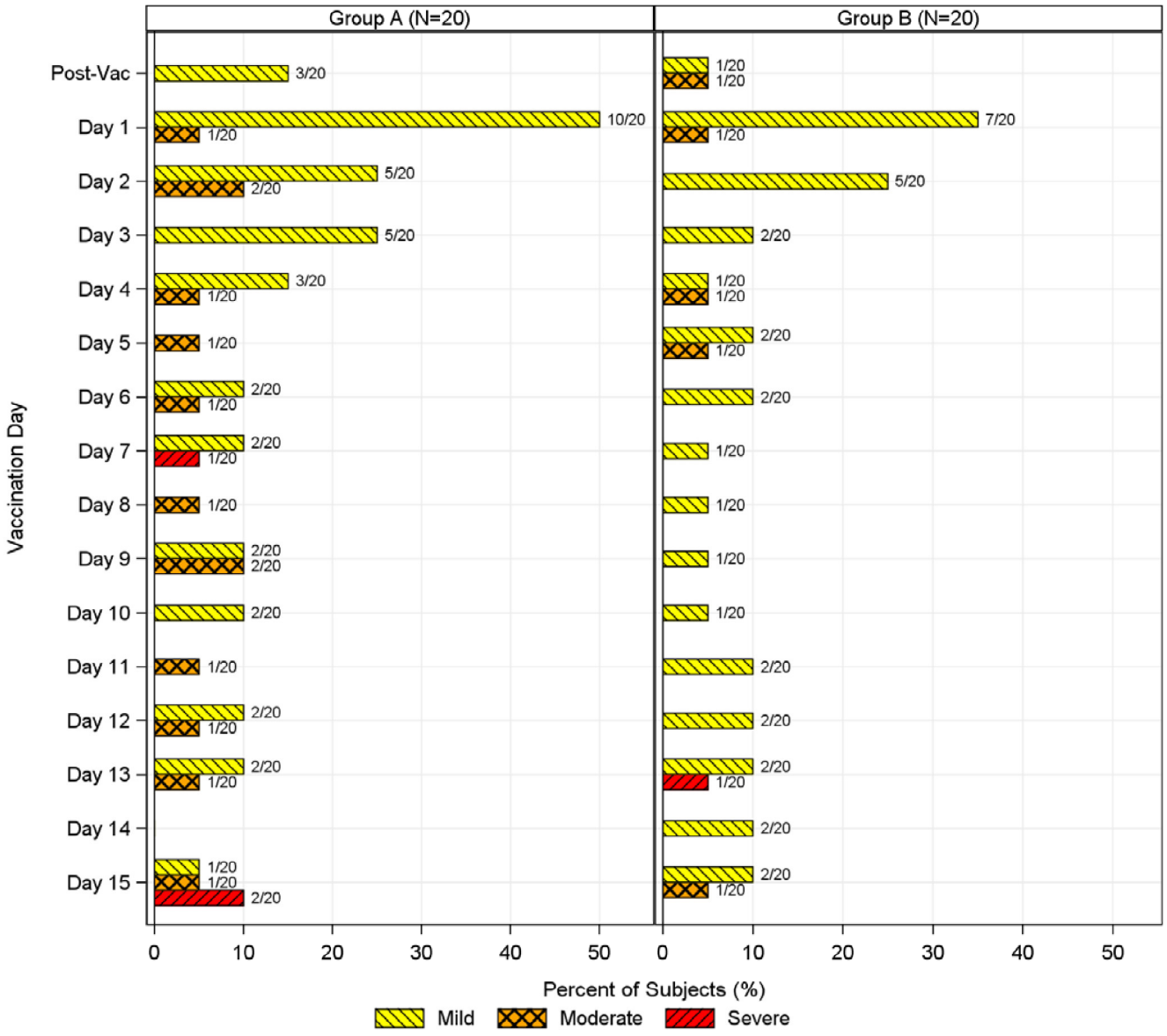


Figure with similar format:

Figure 48: Maximum Severity of Solicited Local Symptoms per Subject by Day Post Treatment, Part B

Figure 49: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, Part A

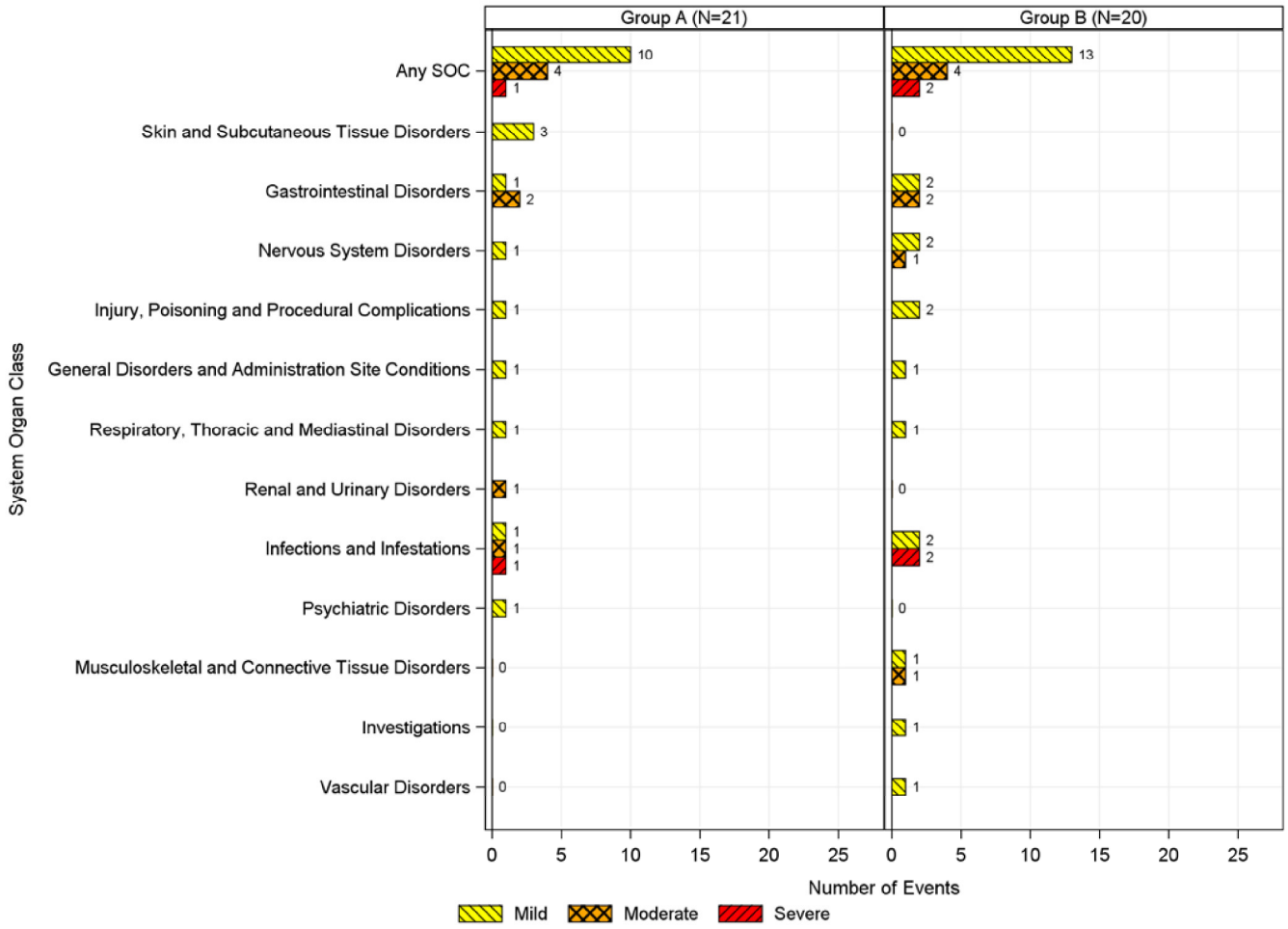


Figure with similar format:

Figure 50: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity, Part B

Figure 51: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity, Part A

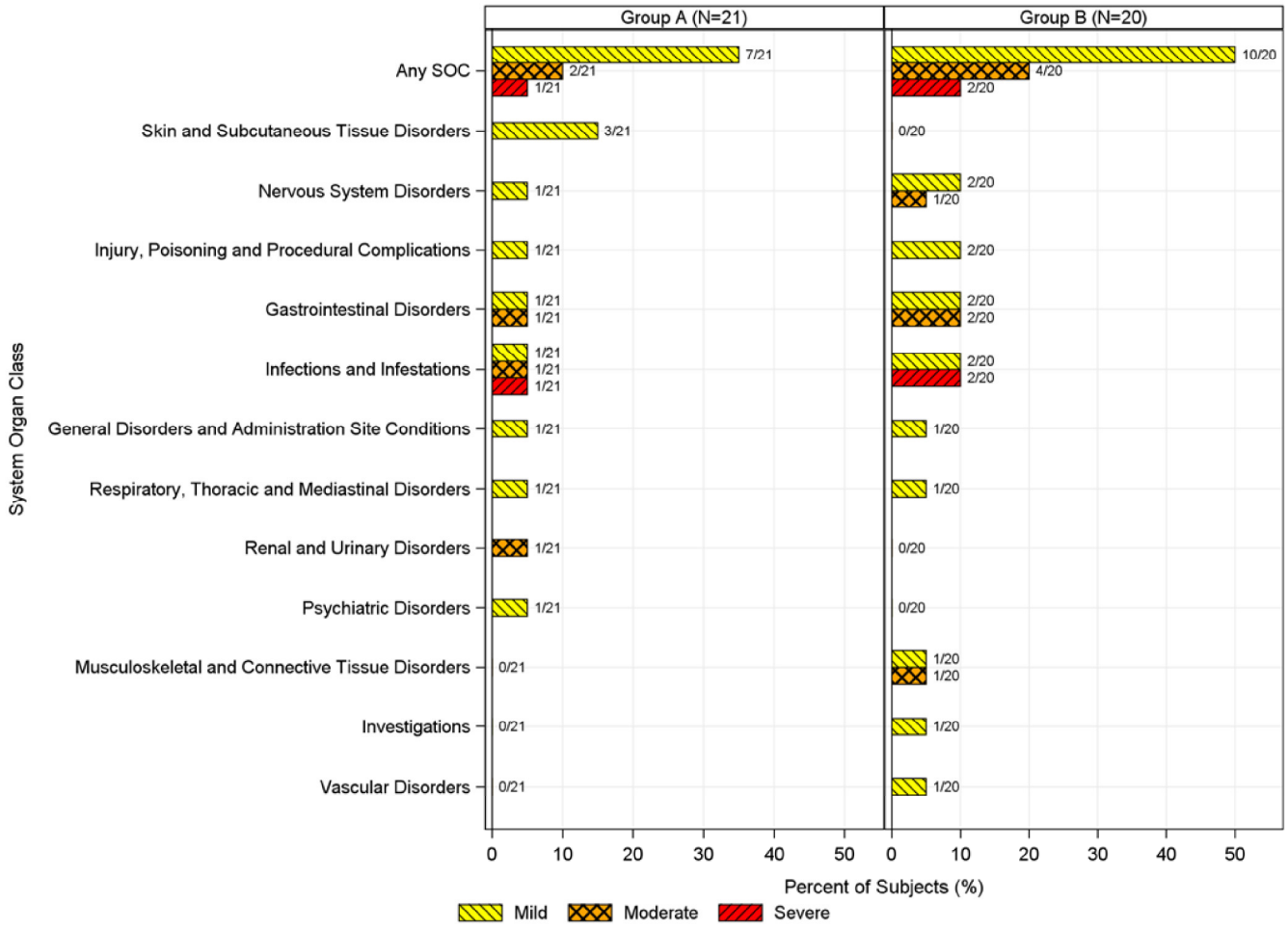


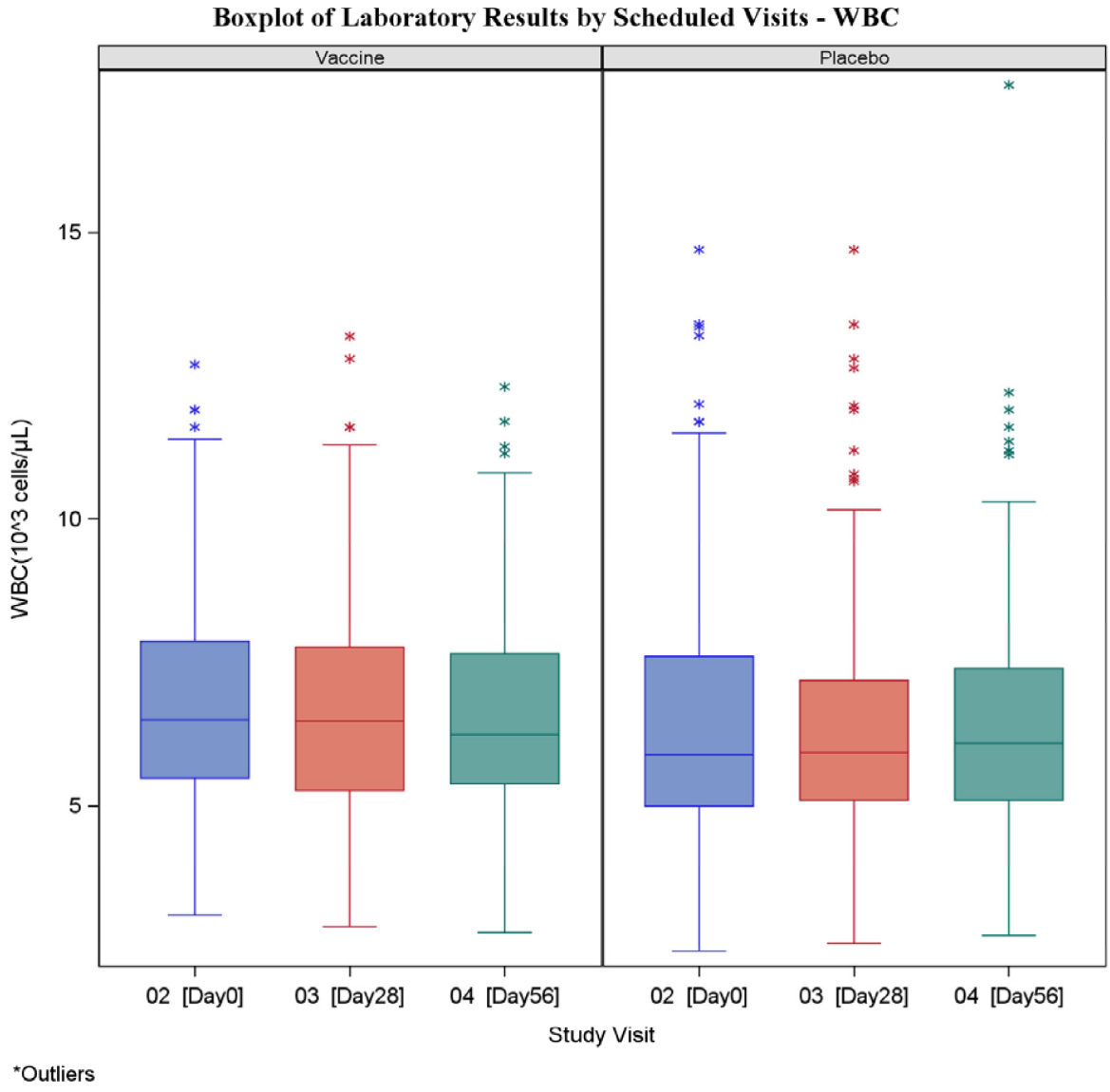
Figure with similar format:

Figure 52: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity, Part B

Figure 53: Incidence of Solicited and Unsolicited Adverse Events by MedDRA® Preferred Term for Adverse Events Reported by 5% or More of Subjects, Part A

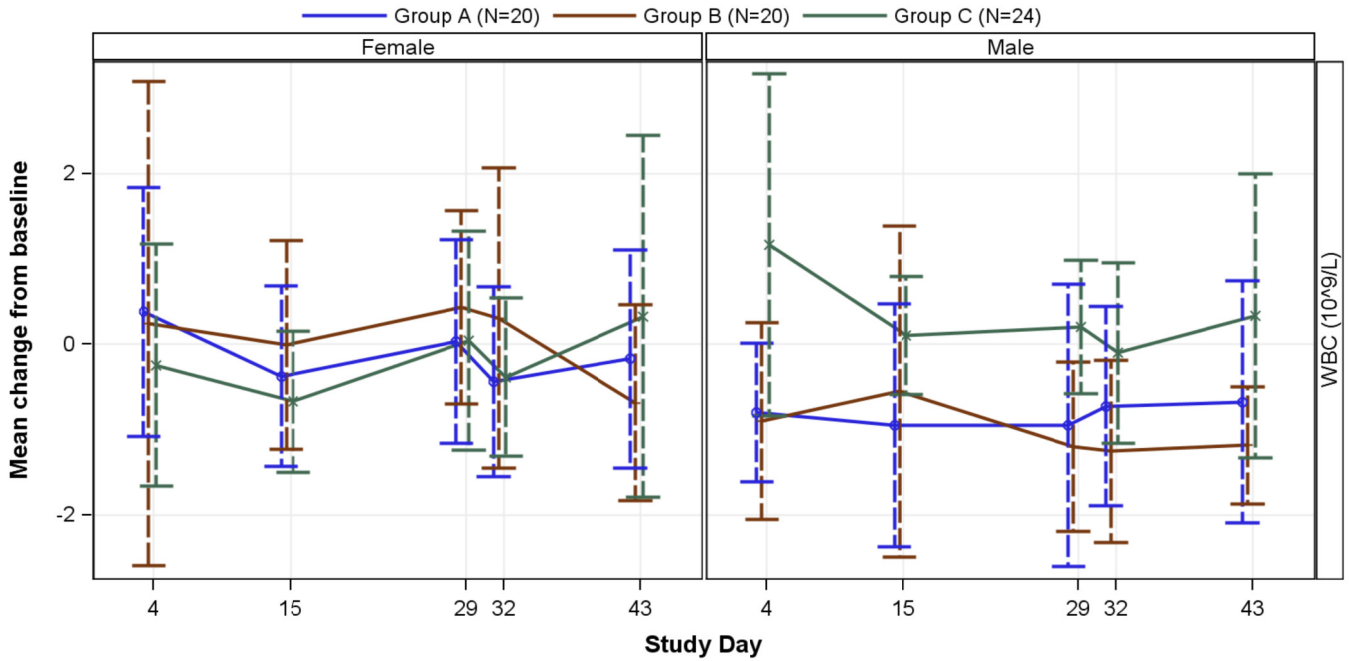
Figure 54: Incidence of Solicited and Unsolicited Adverse Events by MedDRA® Preferred Term for Adverse Events Reported by 5% or More of Subjects, Part B

Figure 55: Boxplot of Laboratory Results by Scheduled Visits, Part A – ALT



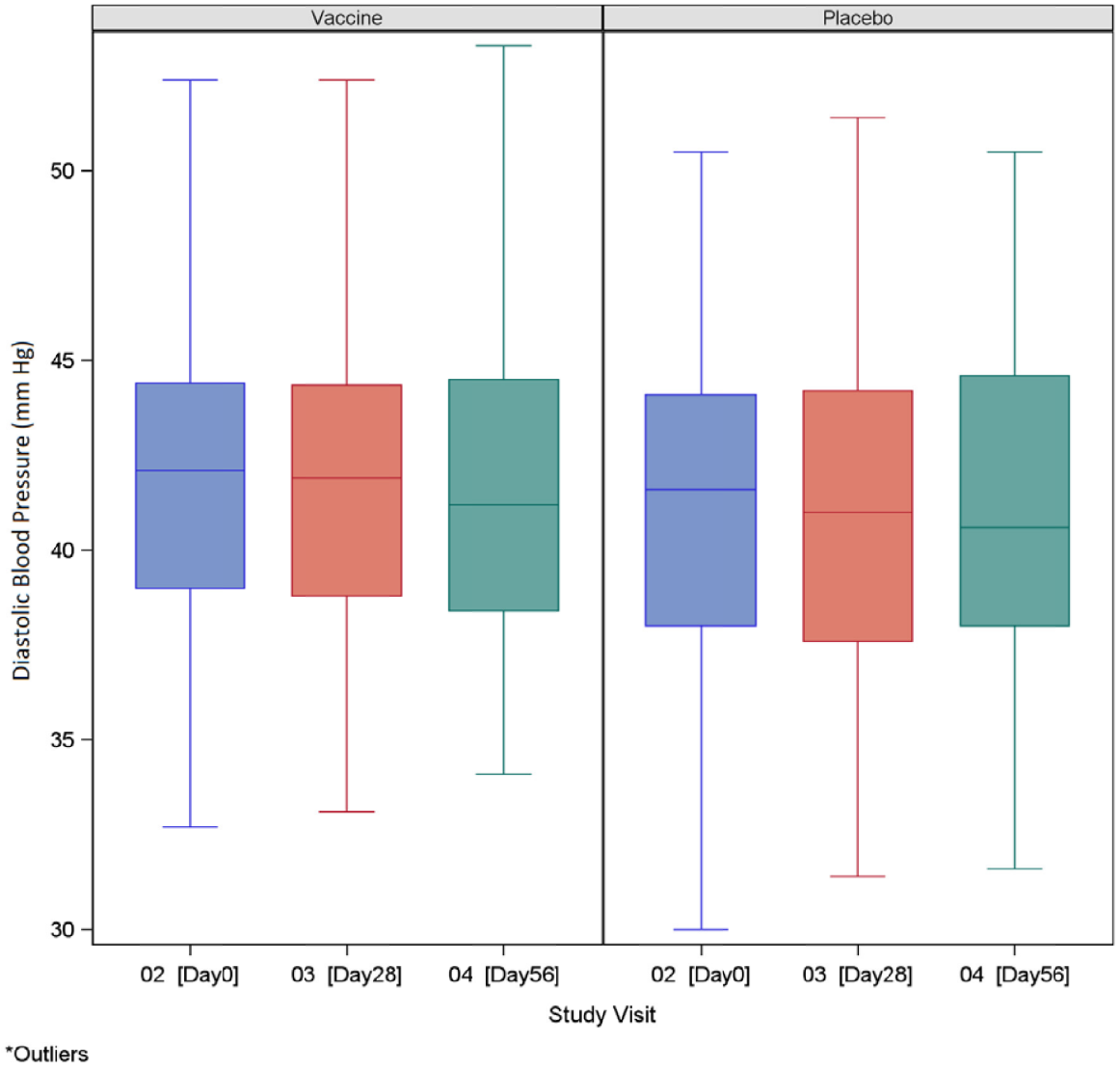
Figures with similar format:

Figure 79: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Sex and Study Group, Part A – ALT



Figures with similar format:

Figure 103: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part A – Systolic Blood Pressure


Vaccine
Placebo
Diastolic Blood Pressure (mm Hg)
50
45
40
35
30
02 [Day0]
03 [Day28]
04 [Day56]
02 [Day0]
03 [Day28]
04 [Day56]
Study Visit
*Outliers

Figures with similar format:

Figure 104: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part A – Diastolic Blood Pressure

Figure 105: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part A – Pulse

Figure 106: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part A – Temperature

Figure 107: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part B – Systolic Blood Pressure

Figure 108: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part B – Diastolic Blood Pressure

Figure 109: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part B – Pulse

Figure 110: Boxplot of Vital Sign Assessments by Scheduled Visits and Study Group, Part B – Temperature

APPENDIX 3: LISTINGS

Listing 1: Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Product Administration Discontinuation	Study Day

Listing with a similar format:

Listing 2: Early Terminations or Discontinued Subjects, Part B

Listing 3: Subject-Specific Protocol Deviations, Part A

Treatment Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing with a similar format:

Listing 4: Subject-Specific Protocol Deviations, Part B

Listing 5: Non-Subject-Specific Protocol Deviations

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

Listing 6: Unanticipated Problems, Part A

Site	Problem Date	Unanticipated Problem Description	Unexpected in Nature, Severity, or Frequency?	Event Related to Participation ?	Subjects or Others at Greater Risk that Previously Known?	Require Report to IRB/EC? If Yes, Date Reported	Event Summary

Listing with a similar format:

Listing 7: Unanticipated Problems, Part B

Listing 8: Subjects Excluded from Analysis Populations, Part A

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, ITT, PP]	[e.g., Safety, ITT, PP, Day x]		
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

Listing with a similar format:

Listing 9: Subjects Excluded from Analysis Populations, Part B

Listing 10: Demographic Data, Part A

Treatment Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing with a similar format:

Listing 11: Demographic Data, Part B

Listing 12: Pre-Existing and Concurrent Medical Conditions, Part A

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

Listing with a similar format:

Listing 13: Pre-Existing and Concurrent Medical Conditions, Part B

Listing 14: Compliance and/or Drug Concentration Data, Part A

Treatment Group	Subject ID	Dose Number	Dose Missed?	Actual [Dosage/Concentration] Administered

Listing with similar format:

Listing 15: Compliance and/or Drug Concentration Data, Part B

Listing 16: Individual Immunogenicity Response Data, Part A

Treatment Group	Subject ID	Vendor Name	Test Category	Date	Study Day	Result

Listing with similar format:

Listing 17: Individual Immunogenicity Response Data, Part B

Listing 18: Individual Efficacy Response Data - ZIKV Endpoints, Part A

Subject ID	Illness Onset Date	PDL						None-PDL		Determined to be ZKIV	Neurological Symptoms	Severity	SAE	Outcome of ZKIV Infection	Illness Resolution Date	Illness Duration (Days)	Co-enroll ZIKV Treatment
		Blood PCR Test 1	Blood PCR Test 2	Blood PCR Test 3	Urine PCR Test 1	Urine PCR Test 2	Urine PCR Test 3	Blood PCR Test	Urine PCR Test								

Listing 19: Individual Efficacy Response Data - ZIKV Signs/Symptoms, Part A

Subject ID	Illness Onset Date	Signs/Symptoms	Summary	Samples Collected for PDL	Determined to be ZKIV	Reported as AE	Medical Term

Listings with similar formats:

Listing 20: Individual Efficacy Response Data - ZIKV Endpoints, Part B

Listing 21: Individual Efficacy Response Data - ZIKV Signs/Symptoms, Part B

Listing 22: Solicited Events – Systemic Symptoms, Part A

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity
				DC		
				Clinic		

[a] DC = Data reported by subject on the Diary Card and reviewed by clinic staff and reported in Diary Card Assessment eCRF.

Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing with similar format:

Listing 23: Solicited Events – Systemic Symptoms, Part B

Listing 24: Solicited Events – Local Symptoms, Part A

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity
				DC		
				Clinic		

[a] DC = Data reported by subject on the Diary Card and reviewed by clinic staff and reported in Diary Card Assessment eCRF.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing with similar format:

Listing 25: Solicited Events – Local Symptoms, Part B

Listing 26: Unsolicited Adverse Events – Part A

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Date of Onset	Severity	SAE?	Relationship to Study Product	Effect on Product Administration Schedule	Outcome	Date of Resolution or Death	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Note: For additional details about SAEs, see Table: xx.											

Listings with similar format:

Listing 27: Unsolicited Adverse Events – Part B

Listing 28: Unsolicited Adverse Events – Screening Segment

Listing 29: Clinical Laboratory Results – Chemistry, Part A

Treatment Group	Subject ID	Visit Number	Date Lab Performed	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listings with similar format:

Listing 30: Clinical Laboratory Results – Chemistry, Part B

Listing 31: Clinical Laboratory Results – Chemistry, Screening Segment

Listing 32: Clinical Laboratory Results – Hematology, Part A

Treatment Group	Subject ID	Visit Number	Date Lab Performed	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listings with a similar format:

Listing 33: Clinical Laboratory Results – Hematology, Part B

Listing 34: Clinical Laboratory Results – Hematology, Screening Segment

Listing 35: Vital Signs, Part A

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Weight (kg)	Height (cm)

Listings with a similar format:

Listing 36: Vital Signs, Part B

Listing 37: Vital Signs, Screening Segment

Listing 38: Concomitant Medications, Part A

Treatment Group	Subject ID	CM Number	Medication	Medication Start Date	Medication End Date (if not ongoing)	Indication	ATC Level 1 (ATC Level 2)

Listing with a similar format:

Listing 39: Concomitant Medications, Part B

Listing 40: Pregnancy Reports, Part A

Treatment Group	Subject ID	Pregnancy Number	Date Site Notified	Start Date of Last Menstrual Period	Gravidity	Parity	Stated Method of Contraception	Date of Delivery or Pregnancy Termination	Estimated Gestational Age	Pregnancy Outcome	If live or still birth, Any Congenital Anomalies or Birth Defects?	If live birth, Neonatal Death?
Comments:												
Comments:												

Listing with similar format:

Listing 41: Pregnancy Reports, Part B