CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 16-0034
Study Title:

Phase I, Randomized, Double-blinded, Placebo-Controlled Dose De-escalation Study to Evaluate the Safety and Immunogenicity of Alum Adjuvanted Zika Virus Purified Inactivated Vaccine (ZPIV) Administered by the Intramuscular Route in Adult Subjects who Reside in a Flavivirus Endemic Area

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Phase I, Randomized, Double-blinded, Placebo-Controlled Dose De-escalation Study to Evaluate the Safety and Immunogenicity of Alum Adjuvanted Zika Virus Purified Inactivated Vaccine (ZPIV) Administered by the Intramuscular Route in Adult Subjects who Reside in a Flavivirus Endemic Area

Protocol Number Code:	**DMID Protocol: 16-0034**
Development Phase:	Phase I
Products:	Adjuvanted Zika Virus Purified Inactivated Vaccine and Normal Saline, 0.9% Sodium Chloride, USP
Form/Route:	Intramuscular injection
Indication Studied:	Zika
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	March 21, 2017
Clinical Trial Completion Date:	August 10, 2021
Date of the Analysis Plan:	07DEC2022
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AFI	Acute Febrile Illness
ALT	Alanine Aminotransferase
ARI	Acute Rash Illness
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Centigrade
CAIMED	Centro Ambulatorio de Investigaciones Medicas
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHIKV	Chikungunya virus
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DENV	Dengue Virus
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DoD	Department of Defense
DRM	Data Review Meeting
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
F	Fahrenheit
FDA	Food and Drug Administration

List of Abbreviations *(continued)*

FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HCT	Hematocrit
HD	High Dose
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention to Treat
JAMA	Journal of the American Medical Association
JEV	Japanese Encephalitis Virus
L	Liter
LD	Low Dose
LLN	Lower Limit of Normal
MAR	Missing at Random
MCAR	Missing Completely at Random
mcg	Microgram
MD	Medium Dose
MedDRA®	Medical Dictionary for Regulatory Activities

List of Abbreviations *(continued)*

mEq	Milliequivalent
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter
mmHg	Millimeters of Mercury
MNAR	Missing Not at Random
MOP	Manual of Procedure
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PBMCs	Peripheral Blood Mononuclear Cells
PFU	Plaque Forming Units
PHI	Protected Health Information
PI	Principal Investigator
PP	Per Protocol
PREP	Public Readiness and Emergency Preparedness
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
RCD	Reverse Cumulative Distribution
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation

List of Abbreviations *(continued)*

SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
TBEV	Tick-borne Encephalitis Virus
U	Units
ULN	Upper Limit of Normal
US	United States
VTEU	Vaccine and Treatment Evaluation Unit
WBC	White Blood Cells
WHO	World Health Organization
WNV	West Nile Virus
WRAIR	Walter Reed Army Institute of Research
YFV	Yellow Fever Virus
ZIKV	Zika Virus
ZPIV	Zika Virus Purified Inactivated Vaccine

1. PREFACE

This Statistical Analysis Plan (SAP) for DMID Protocol 16-0034, "*Phase I, Randomized, Double-blinded, Placebo-Controlled Dose De-escalation Study to Evaluate the Safety and Immunogenicity of Alum Adjuvanted Zika Virus Purified Inactivated Vaccine (ZPIV) Administered by the Intramuscular Route in adult Subjects Who Reside in a Flavivirus Endemic Area*" describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), 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 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 immunogenicity and safety outcomes, and (4) shells of proposed tables and data listings and mock figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. 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

Zika virus (ZIKV) disease (also known as Zika) is an emerging mosquito-borne disease caused by an RNA virus from the family *Flaviviridae,* genus *Flavivirus*. As a Flavivirus, ZIKV is related to the four dengue viruses (DENV 1-4), West Nile virus (WNV), Japanese encephalitis virus (JEV), yellow fever virus (YFV), and tick-borne encephalitic virus (TBEV). The majority of human ZIKV infections result in an asymptomatic infection or a benign, self-limited acute febrile illness. ZIKV infections are characterized primarily by the presence of rash, fever, conjunctivitis, and/or arthralgia, which have been found in the majority of cases seeking care or detected by public health surveillance [8]. In February 2016, the World Health Organization (WHO) declared the emerging ZIKV epidemic a "Public Health Emergency of International Concern." Active mosquito-borne transmission of ZIKV has now been reported in more than 35 countries in South America, Central America, and the Caribbean including Puerto Rico (PAHO 2016).

There is no specific treatment or vaccine currently available to treat or prevent ZIKV infections, other than mosquito control measures. Development of a preventive vaccine against ZIKV infections is a high global public health priority. The ZIKV vaccine used in this trial is a purified inactivated virus vaccine that was produced by the Walter Reed Army Institute of Research (WRAIR). ZPIV is intended to be used in flavivirus endemic areas and among US military members and travelers who may have already received another flavivirus vaccine. Therefore, evaluating the safety and immune response in both flavivirus-naïve and flavivirus-immune subjects is important. This clinical trial was conducted in Puerto Rico, whose population has been exposed to at least the flaviviruses, DENV 1-4 and ZIKV, with potential exposure to WNV in visits to the mainland U.S. and YFV through vaccination. This study setting provides the opportunity to evaluate ZPIV among a largely flavivirus-immune population residing in an area with active ZIKV and DENV transmission.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objectives:

1. Assess the safety and reactogenicity of a homologous prime boost regimen of ZPIV given at two different dose levels in a dose de-escalation format in healthy adult subjects who live in Puerto Rico, a flavivirus endemic area.
2. Compare the safety and reactogenicity profile of ZPIV after each vaccination, between dosage groups, and by pre-vaccination flavivirus immune status.

Secondary Objectives:

1. Assess the humoral immune response to a homologous prime-boost regimen of ZPIV after each dose of vaccine as determined by kinetics of the immune responses, seroconversion rates, and Geometric Mean Titers (GMT) overall, and compare results between dosage groups and by pre-vaccination flavivirus immune status.
2. Assess the durability of the humoral immune response to ZPIV at 6, 12, 18, and 24 months after the second vaccine administration overall, and compare results between dosage groups and by pre-vaccination flavivirus immune status.

Exploratory Objectives

1. Estimate the incidence of ZIKV and DENV infections between Visit 00 and the subject's last visit and describe the clinical presentation including disease severity overall, by dosage group, product received, and pre-vaccination flavivirus immune status.

3.2. Endpoints

Primary Endpoints:

1. Frequency and severity of solicited injection site and systemic reactogenicity from time of study vaccine administration through Day 8 after each administration of study vaccine overall and by dosage group and pre-vaccination flavivirus immune status.
2. Frequency and severity of unsolicited vaccine-related adverse events (AE), including vaccine-related laboratory AE, from first administration of study vaccine until 28 days after the last vaccination overall and by dosage group and pre-vaccination flavivirus immune status.
3. Frequency, type, and duration of serious adverse events (SAE) and adverse events of special interest (AESI) considered related to study vaccine from the first administration of study vaccine until the end of the study overall, and by dosage group and pre-vaccination flavivirus immune status.
4. Frequency of new onset chronic medical conditions reported at any time from the first administration of study vaccine until the end of the study overall, and by dosage group and pre-vaccination flavivirus immune status.
5. Comparison of the frequency, type and duration of vaccine-related Grade 3 local, systemic, or laboratory AE, and Grade 2 or greater local or systemic reactogenicity through Day 8 after each

study vaccine administration between dosage groups and by pre-vaccination flavivirus immune status.

6. Comparison of study withdrawals and discontinuation of study vaccination due to any reason between dosage groups and by pre-vaccination flavivirus immune status.

Secondary Endpoints:

1. Frequency of seroconversion to ZIKV at each post-vaccination visit measured by ZIKV ELISA and neutralization assay in comparison with baseline samples (collected at Visit 00) overall, and by dosage group and pre-vaccination flavivirus immune status.
2. Per Visit GMT as measured by ZIKV ELISA and neutralization assay after each study vaccine administration and for each post-vaccination visit overall, and by dosage group and pre-vaccination flavivirus immune status.
3. Peak GMT as measured by ZIKV ELISA and neutralization assay after each vaccination and overall, and by dosage group and pre-vaccination flavivirus immune status.
4. Proportion of subjects with at least a 4-fold rise in ZIKV GMT as measured by ZIKV ELISA and neutralization assay at 4 weeks after each vaccination compared with baseline overall, and by dosage group and pre-vaccination flavivirus immune status.

Exploratory Endpoints:

1. Number and proportion of subjects who develop an acute febrile illness (AFI) or an acute rash illness (ARI) who have evidence of acute ZIKV or DENV infection detected within 14 days of symptom onset. This endpoint will be analyzed for all subjects overall, and by dosage group, product received, and pre-vaccination flavivirus immune status.
2. Number and severity of laboratory confirmed ZIKV and DENV infections during the study, overall, by treatment group, and pre-vaccination immune status, where severity is described by:
   - Duration of symptoms
   - Grade of symptoms (mild, moderate, severe)
   - Use of concomitant medications
   - Need for hospitalization or other medical care

   Laboratory confirmation will be made by AFI or ARI with either: 1) evidence of acute ZIKV and DENV infection within 14 days of symptom onset or 2) a 4-fold rise in DENV or ZIKV neutralization titers between samples collected at the last visit prior to and at the first visit following the AFI/ARI, where available.

3.3. Study Definitions and Derived Variables

Baseline Values

Unless otherwise specified, baseline values will be defined as the last values obtained prior to the first investigational vaccination. Vital signs (pulse and blood pressure) assessed at screening will be considered as baseline. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an adverse event.

Adverse Events of Special Interest

For this study, Neurologic and Neuroinflammatory Disorders will be considered as adverse events of special interest (AESI). These include Acute Disseminated Encephalomyelitis (ADEM, including site specific variants), Cranial Nerve Disorders (including paralyses/paresis), Guillain-Barre Syndrome (GBS, including Miller Fisher Syndrome and other variants), Immune-mediated Peripheral Neuropathies and Plexopathies, Optic Neuritis, Multiple Sclerosis, Narcolepsy, Transverse Myelitis, meningitis, or meningoencephalitis.

Baseline Flavivirus Immune Status

Subjects enrolled in the study will have blood drawn during the screening visit (Visit 00) or pre-vaccination at the first visit (Visit 01) to determine baseline flavivirus immune status. Serum will be tested via serology for antibodies to ZIKV and DENV. Baseline flavivirus immune status will be treated as a categorical variable and will be used to stratify tables and figures throughout the analyses specified in this SAP. The goal of determining the baseline flavivirus status is to see if there is an effect of baseline flavivirus seropositivity on response to ZPIV. With this in mind, subjects are categorized initially at ZIKV seropositive (based on a positive IgM or IgG assay pre-vaccination) or ZIKV seronegative (based on negative IgM and IgG tests pre-vaccination). Subjects are then subcategorized as DENV seropositive or seronegative, within each ZIKV category.

Baseline flavivirus immune status will be defined primarily as follows:

- ZIKV Seropositive: any subject with detectable ZIKV antibodies pre-vaccination
- ZIKV Seronegative: any subject without detectable ZIKV antibodies pre-vaccination

Baseline flavivirus immune status will then be further classified into the following groups:

- ZIKV Seropositive and DENV Seropositive
- ZIKV Seropositive and DENV Seronegative
- ZIKV Seronegative and DENV Seropositive
- ZIKV Seronegative and DENV Seronegative

Baseline DENV and ZIKV serostatus will be determined via IgM antibody and IgG ELISA assays, with subject results reported as either ‘positive’ or ‘negative’. If a subject has a positive ZIKV result from either the IgM or IgG ELISA assays, they will be considered ZIKV seropositive at baseline. If a subject has inconclusive results for their baseline flavivirus immune status, they will not be included in analyses stratified by baseline flavivirus immune status but will be included in analyses of all subjects.

Post-Baseline Seropositivity

Seropositivity post-baseline is defined as a titer ≥10 and ≥100 for ZIKV MN50 and a titer ≥200 and ≥600 for ZIKV ELISA.

Seroconversion

Seroconversion for ZIKV MN50 titers and ZIKV ELISA titers is defined as ≥4-fold rise from baseline.

Acute Febrile Illness and Acute Rash Illness

Acute febrile illness (AFI) is defined as grade 1 or higher fever on at least 2 consecutive days accompanied by any of the following: new rash not limited to vaccination site, arthralgia, or nonpurulent conjunctivitis. Acute rash illness (ARI) is defined as any new rash not limited to vaccination site.

Laboratory Confirmation of ZIKV or DENV Infection Among Those with AFI or ARI

Among subjects with AFI or ARI, laboratory confirmation of ZIKV or DENV infection will be made by either 1) evidence of acute ZIKV and DENV infection within 14 days of symptom onset (confirmed via PCR) or 2) a 4-fold rise in DENV or ZIKV neutralization titers between samples collected at the last visit prior to and at the first visit following the AFI/ARI illness visit, where available.

Consideration of ZIKV Microneutralization Assay Results in Analysis

The lower limit of quantitation (LLOQ) for ZIKV microneutralization assay results is 10. Any values less than the LLOQ will be assigned a value of 5 by the lab. This imputed value will be used for the purpose of calculating summary statistics such GMT and will be displayed in listings of immunogenicity data. If a subject has a baseline titer below the LLOQ (reported as 5), then they will be considered seroconverted if the post-baseline titer is at least 20 (at least a 4-fold rise). Similarly, a subject with a baseline ZIKV MN50 below the LLOQ will be considered seropositive if the post-baseline titer is at least 10 or 100, as applicable.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This study is a single-center, double-blinded, placebo-controlled, Phase 1, dose de-escalation study to evaluate the safety, reactogenicity, and immunogenicity of a purified inactivated, alum-adjuvanted ZIKV vaccine (ZPIV) administered in a homologous prime-boost regimen to healthy male and non-pregnant female adult subjects living in a flavivirus-endemic area. Two dose levels will be evaluated. Each subject will receive either placebo or 5 mcg (Group 1), or 2.5 mcg (Group 2) of ZPIV administered by IM injection. The study will consist of a screening period of up to 28 days, a vaccination period in which subjects will receive a prime dose of vaccine on Day 1 followed by a homologous boost on Day 29, and a follow-up period of 24 months post boost vaccination. See Table 1 of Appendix 1.

As this is a phase I study, the study will begin with enrollment of two sentinel subjects in Group 1 who will receive 5 mcg ZPIV open label. One sentinel subject will be vaccinated, followed for one day for safety and reactogenicity, and if no halting rules are met per determination of the PI and co-PI, then the second sentinel subject will receive 5 mcg ZPIV open-label. Both sentinels will be followed for safety through Day 8 and if no predefined halting rules are met and no safety concerns are identified, then enrollment of the Group 1 non-sentinel subjects will proceed in double-blind fashion. The same procedure will be used for administration of the boost vaccination to the Group 1 sentinels: 1 sentinel will receive 5 mcg ZPIV open-label, be followed for 1 day for safety and reactogenicity, and if no halting rules are met, then the second sentinel will receive the boost vaccine. Both sentinels will be followed until Day 8 after second vaccination for safety and reactogenicity and if no halting rules are then boost vaccination of the non-sentinel Group 1 subjects can proceed. Enrollment of the 2.5 mcg ZPIV group (Group 2) can begin after or at the same time non-sentinel subjects in Group 1 receive the 1st dose of vaccine.

Solicited local and systemic reactogenicity will be recorded through Day 8 after the prime and boost administration of study vaccine by the subject in a memory aid, and will be reviewed with the clinic staff during clinic visits on Days 2 and 8, and during a telephone visit on Day 4. Safety laboratories will be collected on Days 8 and 15 after administration of the prime and boost dose. Unsolicited AEs will be recorded and evaluated by medical history and targeted physical examinations as needed until 28 days after the second vaccination. SAEs, AESIs, and history of new medical conditions with onset after the first vaccination will be collected for the duration of the study.

Blood will be drawn to evaluate humoral immunity to ZIKV and DENV pre- and at multiple visits post-each vaccination, including baseline serology testing on Visit 00 to determine pre-vaccination flavivirus immune status. CPT tubes will be collected and peripheral blood mononuclear (PBMCs) cells will be harvested and stored for future assessment of immunity including cellular and humoral immunity and systems biology.

Subjects who develop an AFI (grade 1 or higher fever on at least 2 consecutive days accompanied by any of the following: new rash not limited to vaccination site, arthralgia, or nonpurulent conjunctivitis) or ARI (new rash not limited to vaccination site) at any time after signing the ICF until the end of study will be asked to contact the clinic within 3 days of symptom onset and return as soon as possible and at least within 14 days for blood and urine collection to evaluate for acute ZIKV and DENV infection. Subjects will also be asked about any history of AFI and ARI at each clinic visit and phone call after Visit 00. Subjects presenting for evaluation of AFI/ARI will have a medical history including travel

history collected, all symptoms recorded, physical exam if indicated, and concomitant medications and AEs collected, regardless of when the visit occurs.

The schedule of study procedures is displayed in Table 2.

4.2. Discussion of Study Design, Including the Choice of Control Groups

The strategy for the initial development of this vaccine is to conduct a series of phase I studies to assess the safety and immunogenicity in flavivirus-naïve and flavivirus-experienced subjects. Because it is not known how previous exposure to flaviviruses will affect the safety and immunogenicity profile of this vaccine, this strategy will address a critical gap necessary to complete an early and rapid assessment of the viability of this ZIKV vaccine candidate. All trials will initiate with a 5 mcg dose. The first two clinical trials will explore the safety and immune response to the vaccine in flavivirus naïve subjects and in subjects that have been previously vaccinated with JEV or YFV vaccines. This trial will be conducted in Puerto Rico, whose population has been exposed to DENV 1-4, ZIKV and potentially YFV and/or WNV. A fourth clinical trial will be conducted by Beth Israel Deaconess Medical Center to evaluate the safety and immunogenicity of an accelerated vaccination schedule with the Zika vaccine candidate in healthy adults. The initial doses and regimens that will be utilized in these initial trials was selected based on experience with other inactivated flavivirus vaccines and recent data from mouse and NHP studies. Experience with licensed flavivirus vaccines suggests a 5 mcg dose should be safe and immunogenic; the 5 mcg dose was safe and protective in a NHP model [1]. Therefore, for these trials, subjects will be enrolled initially in the 5 mcg group. To determine if lower doses of ZPIV are equally or comparably immunogenic to the 5 mcg dose, subjects in this trial will then be enrolled in the 2.5 mcg group, or in a 1.25 mcg group in other trials. ZPIV is intended to be used in flavivirus endemic areas and among US military members and travelers who may have already received another flavivirus vaccine. Therefore, evaluating the safety and immune response in both flavivirus-naïve and flavivirus-immune subjects is important. This study provides the opportunity to evaluate ZPIV among a largely flavivirus-immune population who resides in an area with active ZIKV and DENV transmission.

4.3. Selection of Study Population

Approximately ninety subjects, males and non-pregnant, non-breastfeeding females, 21-49 years of age, inclusive, who are in good health (based on physical examination, medical history and clinical judgment) and meet all eligibility criteria, will be enrolled. The study population's racial and ethnic make-up should reflect the demographics of the larger community at the clinical trial site.

4.3.1. Subject Inclusion Criteria

Subjects eligible to participate in this study must meet all of the following inclusion criteria:

1. Must be a male or non-pregnant, non-breastfeeding female between the age of 21 and 49 years, inclusive at the time of screening and enrollment.
2. Must be willing and able to read, sign and date the informed consent document before study related procedures are performed.
3. Must be willing and able to comply with study requirements and available for follow-up visits for the entire study.
4. Must have a means to be contacted by telephone.

5. Must have a body mass index (BMI) ≥18.1 and <35.0 kg/m^2.
6. Must have acceptable* screening laboratory findings within 28 days before enrollment.

   **Acceptable clinical laboratory parameters include:*

   -Hemoglobin: women: ≥11.5 g/dL; men ≥13.5 g/dL
   -Hematocrit: women: ≥ 34.5%; men ≥ 40.5%
   -White blood cell count: ≥3.500 cells/mm^3 but ≤10,800 cells/mm^3
   -Platelets: ≥150,000 but ≤450,000 per mm^3
   -Urine dipstick (clean urine sample): protein <1+, glucose negative
   -Serum creatinine ≤1 x institutional upper limit of normal (ULN)
   -Blood urea nitrogen (BUN) <25
   -Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <1.25 x institutional ULN
   -Total bilirubin <1.25 x institutional ULN

   **Note: If laboratory screening tests are out of acceptable range, repeat of screening tests is permitted once, provided there is an alternative explanation for the out of range value.*
7. Must be in good health based on the investigator's clinical judgment when considering findings from past medical history, medication use, vital signs, and an abbreviated physical examination.

   Note 1: Good health is defined by the absence of any medical condition described in the exclusion criteria in a subject with a normal abbreviated physical exam and vital signs. If the subject has a preexisting condition not listed in exclusion criteria, it cannot meet any of the following criteria: 1.) first diagnosed in last 3 months; 2.) worsening in terms of clinical outcome in last 6 months; or 3.) involves need for medication that may pose a risk to subject's safety or impede assessment of adverse events or immunogenicity if they participate in study.

   Note 2: An abbreviated physical exam differs from a complete exam in that it does not include a genitourinary and rectal exam.

   Note 3: Vital signs must be normal by protocol toxicity grading scale or determined to be normal-variant by investigator. In the event of an abnormal heart rate or blood pressure due to physiological variation or activity, the subject may rest for 10 minutes in a quiet room, and then blood pressure and/or heart rate may be re-measured. Repeated vital signs may be used to determine eligibility.
8. Women of childbearing potential* must have a negative serum pregnancy test at screening and a negative urine pregnancy test immediately prior to each vaccination.

   Note: All female subjects are considered of childbearing potential unless postmenopausal or surgically sterilized and ≥3 months have passed since sterilization procedure. Postmenopausal is defined as amenorrhea for ≥12 months without an alternative medical cause. Permanent female sterilization procedures include tubal ligation, bilateral salpingectomy, hysterectomy, bilateral oophorectomy, or successful Essure placement.
9. Women of childbearing potential must use an acceptable method of contraception* from one month (30 days) prior to the first vaccination until the end of the study.

   **Acceptable methods of contraception include the following:*

-Use highly effective contraceptive methods, defined by <1% failure rate per year independent of user adherence, including long-acting reversible contraception (LARC): progestin-releasing subdermal implants and intrauterine devices (IUD), OR
-Use effective contraceptive methods, defined by 5-9% failure rate with typical use and <1% failure rate with consistent and correct use, including: prescription oral contraceptives, contraceptive injections, combined pill, progestin-only pill, hormone-releasing transdermal patch or vaginal ring, and depot medroxyprogesterone acetate injection (Depo-Provera), OR
-Male sex partners must have had a vasectomy ≥3 months prior to first vaccination, OR
-Practice abstinence defined as refraining from heterosexual intercourse from 30 days before first vaccination until the end of the study.

10. Female subjects must agree to not donate eggs (ova, oocytes) from the start of screening period until the end of the study.
11. Subjects must provide concurrent consent at the time of enrollment and 1st vaccination to future use of stored blood samples to measure immunity to ZIKV.

4.3.2. Subject Exclusion Criteria

Subjects eligible to participate in this study must not meet any of the following exclusion criteria:

1. Has plans to become pregnant during the course of the study or is currently pregnant or breastfeeding.
2. Plans to receive a licensed flavivirus vaccine or participate in another flavivirus vaccine trial during the study.
3. Has positive serology for HIV 1/2, Hepatitis C virus, or Hepatitis B surface antigen.
4. Has known or suspected congenital or acquired immunodeficiency, or recent history or current use of immunosuppressive therapy*

   **Anti-cancer chemotherapy or radiation therapy within the preceding 6 months, or long-term (at least 2 weeks within the previous 3 months) systemic corticosteroids therapy (at a dose of at least 0.5 mg/kg/day). Intranasal or topical prednisone (or equivalent) is allowed.*
5. Had organ and/or stem cell transplantation whether or not on chronic immunosuppressive therapy.
6. Has history of malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision that is considered to have achieved cure*.

   **Subjects with a history of skin cancer must not be vaccinated at the previous tumor site.*
7. Has history of chronic or acute severe neurologic condition*.

   **Including history of Guillain-Barre syndrome, seizure disorder or epilepsy, Bell's palsy, meningitis, or disease with any focal neurologic deficits.*
8. Has diabetes mellitus type 1 or type 2, including cases controlled with diet alone.

   **Note: history of isolated gestational diabetes is not an exclusion criterion.*
9. Has history of thyroidectomy, or thyroid disease requiring medication during the last 12 months.

10. Has major psychiatric illness during last 12 months that in the investigator's opinion would preclude participation.
11. Has history of other chronic disease or condition*.

    **Includes the conditions and diagnoses defined as AESI in Section 9, as well as autoimmune disease, hypercholesterolemia, chronic hepatitis or cirrhosis, chronic pulmonary disease, chronic renal disease, and chronic cardiac disease including hypertension even if medically controlled*

    – Vital signs must be normal by protocol toxicity grading scale or determined to be normal-variant by investigator. In the event of an abnormal heart rate or blood pressure due to physiological variation or activity, the subject may rest for 10 minutes in a quiet room, and then blood pressure and/or heart rate may be re-measured. Repeated vital signs may be used to determine eligibility.
12. Has current or past history of substance abuse that in the investigator's opinion would preclude participation.
13. Has tattoos, scars, or other marks on both deltoid areas that would, in the opinion of the investigator, interfere with assessment of the vaccination site.
14. Has a history of chronic urticaria (recurrent hives).
15. Has known allergy or history of anaphylaxis or other serious reaction to a vaccine or vaccine component*.

    **Including aluminum hydroxide (alum) or aminoglycosides (e.g., neomycin and streptomycin).*
16. Had major surgery (per the investigator's judgment) in the month prior to screening or plans to have major surgery during the study.
17. Received blood products or immunoglobulin in the 3 months prior to screening or planned use during the course of the study.
18. Donated a unit of blood within 8 weeks before Day 1 or plans to donate blood during the course of the study.
19. Received live attenuated vaccine from 30 days before Day 1 or plans to receive a live attenuated vaccine from Day 1 until 30 days after the last vaccination.
20. Received killed or inactivated vaccine from 14 days before Day 1 or plans to receive a killed or inactivated vaccine from Day 1 until 14 days after the last vaccination.
21. Received experimental therapeutic agents within 3 months prior to the first study vaccination or plans to receive any experimental therapeutic agents during the course of the study.
22. Is currently participating or plans to participate in another clinical study involving an investigational product, blood drawing, or an invasive procedure listed below.

    **An invasive procedure requiring administration of anesthetics or intravenous dyes or removal of tissue would be excluded. This includes endoscopy, bronchoscopy, or administration of IV contrast.*
23. Has an acute illness or temperature ≥38.0ºC on Day 1 or Day 29* or within 2 days prior to vaccination.

**Subjects with fever or an acute illness on the day of vaccination or in the 2 days prior to vaccination may be re-assessed and enrolled if healthy or only minor residual symptoms remain within 2 days of Day 1 or Day 29.*

24. Is a study site employee* or staff paid entirely or partially by the OCRR contract or subcontract for the trial, or staff who are supervised by the PI or Sub-Investigators.

    **Including the Principal Investigator, sub-Investigators listed in Form FDA 1572 or Investigator of Record Form*

25. In the investigator's opinion, the subject cannot communicate reliably, is unlikely to adhere to the study requirements, or has a condition that would limit their ability to complete the study.

4.4. Treatments

4.4.1. Treatments Administered

All subjects were to receive two doses of either 5 mcg ZPIV, 2.5 mcg ZPIV, or placebo administered intramuscularly 28 days apart.

4.4.2. Identity of Investigational Product(s)

ZPIV (Puerto Rico PRVABC59 strain), a formalin-inactivated whole virus vaccine produced by WRAIR, was administered in two intramuscular (IM) injections 28 days apart. Aluminum Hydroxide Adjuvant Alhydrogel® (aluminum hydroxide [or alum]) was used to adjuvant the ZPIV vaccine and to further dilute the adjuvanted vaccine for the 2.5 mcg dose. Use of alum as an adjuvant is well established and generally well tolerated.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Enrollment/randomization was performed through the enrollment module of AdvantageEDC, the electronic data capture system maintained by the SDCC. The list of randomized treatment assignments was prepared by statisticians at the SDCC and included in the enrollment module for this trial. The electronic data capture system assigned each subject a treatment code after the demographic and eligibility data have been entered into the system. A designated individual at each site was provided with a treatment key, which links the treatment code to the actual treatment assignment, to be kept in a secure place.

At the time of consent and upon entry of demographic data and confirmation of eligibility for this trial, the subject is enrolled. In group 1 (5 mcg ZPIV, N=45; placebo, N=5), two sentinel subjects were enrolled first and received ZPIV in an open-label fashion. All other subjects were randomized in a double-blind fashion. Upon completion of enrollment in Group 1, Group 2 subjects (2.5 mcg ZPIV, N=35; placebo, N=5) were randomized. Subjects received the same study product at their first and second investigational vaccinations.

4.4.4. Selection of Doses in the Study

Experience with licensed flavivirus vaccines suggests a 5 mcg dose should be safe and immunogenic; the 5 mcg dose was safe and protective in a NHP model [1]. Therefore, for this trial, subjects were enrolled initially in the 5 mcg group. To determine if lower doses of ZPIV are equally or comparably immunogenic to the 5 mcg dose, subjects were then enrolled in the 2.5 mcg group.

4.4.5. Selection and Timing of Dose for Each Subject

All subjects were scheduled to receive the assigned vaccination on Day 1 and Day 29 (±3).

4.4.6. Blinding

This is a double-blinded study with the exception of the two sentinel subjects in Group 1. Non-sentinel subjects in Group 1, all subjects in Group 2, investigators, study personnel performing any study-related assessments following study vaccine administration, and laboratory personnel performing assays are blinded to study treatment within a group. The two sentinel subjects received open-label 5.0 mcg ZPIV (i.e., sentinels, investigators and study personnel were not blinded to sentinel study treatment). Laboratory testing personnel remain blinded to the identity and timepoint of individual samples.

The unblinded study vaccine administrator(s) is a study clinician credentialed to administer vaccines but is not involved in study-related assessments or have subject contact for data collection following study vaccine administration.

4.4.7. Prior and Concomitant Therapy

Assessment of study eligibility included a review of all permitted and prohibited medications per the subject inclusion and exclusion criteria. Prescription and over-the-counter drugs and vaccines were recorded, as well as herbals, vitamins, and supplements. Pre-study and concomitant use of any medications, therapies, or vaccines were reported. Medications included all current medications and non-study vaccinations taken within 30 days prior to signing the ICF through approximately Day 29 after the last study vaccination. Subjects who do not receive all study vaccinations would have concomitant medications collected through approximately Day 29 after the last study vaccination, or early termination, whichever occurs first. Subjects presenting with a history of AFI or ARI would have all concomitant medications taken since start of illness recorded.

Medications that might interfere with the evaluation of the investigational vaccine should not be used during the study period unless necessary. Medications in this category include the prohibited medications per the subject exclusion criteria. In addition, the site principal investigator or appropriate sub-investigator may identify other medications that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity. Use of medications as prophylaxis prior to study vaccination was prohibited.

4.4.8. Treatment Compliance

All subjects were to receive a prime dose of vaccine on Day 1 followed by a homologous boost on Day 29. All doses of vaccine were administered in the clinic by a vaccine administrator(s) credentialed to administer vaccines.

4.5. Immunogenicity and Safety Variables

In general, multiple observations within a specific visit period were accepted. In the case of multiple observations within a specific window, the assessment value closest to the scheduled visit date will be used in the analyses for the post-baseline records. If observations have the same distance to the scheduled assessment, the latest one will be used. Unless otherwise specified, the last assessment value recorded prior to the prime dose will be used as baseline. All the recorded data will be listed. Samples from days on which a subject was vaccinated were collected prior to vaccination.

All subjects were to have venous blood samples for assessment of humoral immunity collected on Days 1, 15, 29, 43, 57, 209, 388, and 569. Assay results are reported as the ZIKV titers giving 50% reduction in viral infection (MN50) and IgG ELISA titers. DENV neutralization titers were also to be recorded in subjects reporting ARI or AFI. Samples from the immunogenicity visits immediately before and after the illness visit were used to measure DENV titers, which will be used to aid laboratory confirmation of ZIKV/DENV infection.

Solicited adverse events were collected from the time of study vaccine administration through Day 8 after each dose. Subjects received a memory aid to record any solicited AEs on each day. The following injection site reactogenicity events were measured and grading according to the scale in Table 3 and Table 4: pain, tenderness, pruritis, ecchymosis, erythema, and induration. The following systemic solicited events were measured and graded according to the scale in Table 4 and Table 5: feverishness, fatigue, malaise, myalgia, arthralgia, headache, nausea, vomiting, diarrhea, abdominal pain, rash, and fever.

Vital signs of heart rate and blood pressure were measured in subjects at Days 1, 2, 8, 15, 29, 30, 36, 43, and 57. The measurements were assessed for adverse events of bradycardia/tachycardia and systolic and diastolic hypotension/hypertension according to the scale in Table 6.

Venous blood and urine were collected from subjects on Day 8 and Day 15 following each vaccination for safety clinical laboratory tests. The tests include WBC, hemoglobin, hematocrit, and platelets, ALT, AST, total bilirubin, BUN, creatinine, and urine dipstick for protein and glucose. Laboratory values were assessed for adverse events according to the grading scale in Table 7. Unsolicited adverse events were collected from all subjects through Day 57 (28 days after the 2nd vaccination). These events were assessed for severity and relatedness to study product. Serious adverse events (SAE), adverse events of special interest (AESI), and new onset chronic medical conditions (NOCMC) were collected for the duration of each subject's follow-up. Adverse events of special interest (AESI) for this study are neurologic and neuroinflammatory disorders collected through the duration of the subject's follow-up period.

Subjects were observed for development of an AFI/AFI and all related adverse events from the time of signing the informed consent form through follow-up. Subjects who reported an ARI/AFI were assessed for the following symptoms which are graded on a scale from 1 (least severe) to 3 (most severe): fever, feverishness, lethargy, restlessness, rash not at injection site, nonpurulent conjunctivitis, headache, shortness of breath, retino-orbital pain, myalgia, arthralgia, arthritis, nausea, abdominal pain, vomiting (evaluated for presence only), and bleeding (evaluated for presence only).

5. SAMPLE SIZE CONSIDERATIONS

The sample size for this study was selected to obtain preliminary estimates of vaccine safety and immunogenicity in a time sensitive manner. This study was not designed to test a specific null hypothesis. As this is a phase I study of ZPIV, it is primarily designed to collect initial information about safety and immune responses of two different doses of the vaccine.

The sample size in each dose cohort is small, thus the precision of estimates for AEs is limited. Rare AEs associated with dose are not demonstrable in a clinical study of this size; however, the probabilities of observing one or more AEs within a dose group at the minimum dose sample size of 35 and among the approximately 80 subjects receiving ZPIV are presented in Table 8. The minimum detectable event rates to achieve various levels of power are also displayed in Table 9.

If there are AEs associated with a particular dose of ZPIV, this study will have at least 80% power to observe at least one such event in a dose cohort if the true rate is 4.5%. If there are AEs associated with ZPIV overall, independent of dose, this study will have approximately 80% power to observe at least one such event in all ZIKV vaccine subjects if the true rate is 2.0%.

The study enrollment plan was modified in protocol amendment 5.0 (18 December 2018) to address the loss of evaluable subjects in Group 1 and delay of enrollment due to Hurricane Maria. The original study design planned to enroll 40 ZPIV recipients and 5 placebo recipients in each Group. Due to Hurricane Maria, 11 subjects enrolled in Group 1 had loss of samples at key timepoints. To rebalance the number of evaluable subjects between Groups, Group 1 enrollment was increased by 5 subjects and Group 2 enrollment was decreased by 5 subjects, for a total enrollment of 50 subjects in Group 1 and 40 in Group 2. Treatment assignments for both groups are assigned according to the originally planned 8:1 ratio of ZPIV:placebo.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, minimum and maximum, unless otherwise specified. The frequency and percentage of observed levels will be reported for all categorical measures; denominators for percentages will be defined for each analysis.

Listings will be provided for all data. Sort order will be specified on each listing shell in Appendix 3.

Summary tables will be structured with a column for each treatment group (2.5 mcg ZPIV, 5 mcg ZPIV, Placebo) and for all subjects for safety summaries.

All tables will be annotated with the total population size relevant to that table/group, including any missing observations.

6.2. Timing of Analyses

This study has 3 planned interim analyses, all of which were to be performed on cleaned, monitored and locked datasets. The first two interim analyses were to consider safety, reactogenicity, and immunogenicity data and to take place at the following time points:

- The first interim analysis would take place after the last subject in Group 1 had been followed through 28 days post-second ZPIV administration (Day 57) and the first interim database had been locked.
- The second interim analysis would take place after the last subject in Group 2 had been followed through 28 days post-second ZPIV administration (Day 57) and the second interim database had been locked.
- The third interim analysis would describe the incidence and severity of AFI/ARI after all subjects had completed one-year follow-up after the 2nd vaccination.

The second and third interim analyses were performed at the same time, thus two separate interim analyses occurred prior to the CSR, dated 12DEC2018 and 22DEC2020. The analyses performed for the interim analyses were described in a separate Statistical Analysis Plan, "Interim Statistical Analysis Plan for DMID Protocol: 16-0034 v1.0" dated 01OCT2018.

The final analysis will be presented in the Clinical Study Report which will occur after all safety and protocol-specified humoral immunogenicity results, including all primary and secondary endpoint data, collected through Day 750 are available and the database has been locked. Given the urgency to obtain data in a timely manner, additional humoral and cellular immunogenicity assessments could be summarized in one or more addenda to the main CSR.

6.3. Analysis Populations

Three analysis populations are defined: safety, immunogenicity, and per-protocol. In the case of mis-randomization or treatment administration error, subjects in all analysis populations will be analyzed according to the study vaccine received.

6.3.1. Safety Population

The Safety population will include all subjects who receive at least one study vaccination.

6.3.2. Immunogenicity (IMM) Population

The immunogenicity population will include all subjects who receive at least one study vaccination and contribute both pre- and at least one post-study vaccination sample for immunogenicity testing for which valid results are reported. Subjects with a loss of samples at pre-vaccination timepoints due to the natural disaster (i.e., Hurricane Maria) will be excluded from the GMFR and seroconversion analysis but will be included in post-baseline immunogenicity analyses where available. This population will be used for analysis of all immunogenicity data.

6.3.3. Per-Protocol (PP) Population

The Per Protocol (PP) population includes all subjects in the immunogenicity population with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits subsequent to major protocol deviations, such as:
  - Second vaccination not received,
  - Second vaccination received out of window,
  - Receipt of non-study licensed live vaccine within 30 days prior to or after each study vaccination,
  - Receipt of non-study licensed inactivated vaccine within 14 days prior to or after each study vaccination,
  - Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after each study vaccination.
- Data from any visit that occurs substantially out of window.

The Per Protocol population may differ across post-vaccination visits and denominators will be the number of samples tested and included in the analysis at each visit.

6.4. Covariates and Subgroups

As well as treatment group, subjects will additionally be classified by baseline flavivirus immune status, defined primarily as follows:

- ZIKV Seropositive: any subject with detectable ZIKV antibodies pre-vaccination
- ZIKV Seronegative: any subject without detectable ZIKV antibodies pre-vaccination

Baseline flavivirus immune status will then be further classified into the following groups:

- ZIKV Seropositive and DENV Seropositive
- ZIKV Seropositive and DENV Seronegative
- ZIKV Seronegative and DENV Seropositive
- ZIKV Seronegative and DENV Seronegative

If a subject has inconclusive results for baseline flavivirus immune status, they will not be summarized with either subgroup defined above but will be included in summaries of all subjects pooled.

Subgroups based on baseline flavivirus immune status will be used in analysis of the secondary and exploratory endpoints only. For all tables and figures presenting group-aggregate analyses by subgroup—or any columns, rows, or panels within them—a single stratum must include at least two subjects in order to be generated.

6.5. Missing Data

No imputation will be performed for missing values. Missing data are assumed to be missing completely at random.

6.6. Interim Analyses and Data Monitoring

This study has 3 planned interim analyses as described in Section 6.2. Summaries described for the second and third interim reports were combined into a single report thus a total of 2 interim analyses were actually performed. The analyses performed for the interim analyses were described in "Interim Statistical Analysis Plan for DMID Protocol: 16-0034 v0.1." No unblinding of any individual subject treatment will be released in any interim analysis. Interim analyses will not include any formal hypothesis testing. They will, however, be made available to the study team and may impact the course of this study, be published, or be used in the planning of future studies.

6.7. Multicenter Studies

Not applicable.

6.8. Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons/multiplicity were planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A flowchart showing the disposition of study subjects, adapted from the CONSORT Statement will be included in Figure 1. This figure will present the number of subjects assesses for eligibility, randomized, terminated early, and included in the safety, immunogenicity, and per protocol populations. The CONSORT diagram will be presented by treatment group.

The disposition of subjects in the study will be tabulated by treatment group (Table 11). The table will include the number of subjects screened, enrolled/randomized, vaccinated, discontinued dosing, terminated early, completed follow-up and completed the study per-protocol. Listing 2 includes subjects who terminated early or discontinued from the study.

Between-group comparisons of the numbers of subjects overall and by baseline flavivirus status who withdrew early and the numbers who discontinued treatment (i.e., did not receive the second dose) will be presented in Table 12 using Fisher's exact 2-tailed test.

The number and percent of subjects excluded from each analysis population will be presented in Table 13 by treatment group and reason for exclusion. The number of subjects included in each immunogenicity summary will be presented in Table 14 by analysis population, treatment group, and immunogenicity time point. A listing of subjects excluded from analysis populations is available in Listing 5.

Dates of first treatment administration will be listed by treatment group in Table 15 and reasons for screen failure will be summarized in Table 16.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 10). All subject-specific protocol deviations and non-subject-specific protocol deviations will be included as data listings (Listing 3 and Listing 4).

8. IMMUNOGENICITY EVALUATION

8.1. Primary Immunogenicity Analysis

Not applicable.

8.2. Secondary Immunogenicity Analyses

8.2.1. ZIKV Microneutralization Antibodies (MN50)

Seropositivity rates will be calculated based on ZIKV MN50 titers ≥10 and ≥100. Seroconversion rates will be calculated based on the number of subjects experiencing at least a 4-fold rise in ZIKV MN50 titers from baseline.

Geometric mean titer (GMT) and 95% CI for ZIKV MN50 results at each visit and for peak titer results will be summarized by treatment group overall and by baseline flavivirus immune status for the immunogenicity (IMM) population in Table 20 and per protocol (PP) population in Table 21.

Geometric mean fold rise from baseline (GMFR) and 95% CI results at each post-baseline visit and for each subject's peak ZIKV MN50 titer results will be summarized by treatment group overall and by baseline flavivirus immune status for the IMM population in Table 22 and PP population in Table 23.

Seropositivity rates and 95% CIs at each visit and for peak ZIKV MN50 titer results will be summarized by treatment group overall and by baseline flavivirus immune status for the IMM population in Table 24 and PP population in Table 25.

Seroconversion rates and 95% CI at each post-baseline visit and using peak titer results will be presented by treatment group overall and by baseline flavivirus immune status for the IMM population in Table 26 and PP population in Table 27. Denominators for percentages will be the number of subjects with non-missing data at the applicable time point and 95% CI will be calculated using Clopper-Pearson methodology from a binomial distribution.

Graphical presentations of immune response by treatment group and baseline flavivirus immune status will include reverse cumulative distribution curves (Figure 2 through Figure 11 and longitudinal presentation of GMTs (Figure 16 and Figure 17), seropositivity at a threshold of ≥10 (Figure 18 and Figure 19), seropositivity at a threshold of ≥100 (Figure 20 and Figure 21), and percent seroconversion (Figure 22 and Figure 23).

A listing of ZIKV MN50 titers by subject, treatment group, baseline flavivirus immune status, planned time point, and actual study day is presented in Listing 8.

8.2.2. ZIKV ELISA Antibodies

Seropositivity rates will be calculated based on ZIKV IgG ELISA titers ≥200 and ≥600. Seroconversion rates will be calculated based on the number of subjects experiencing at least a 4-fold rise in ZIKV IgG ELISA titers from baseline.

The analyses described in Section 8.2.1 will be repeated for ZIKV ELISA titers: GMT and 95% CI results are presented in Table 28 (IMM) and Table 29 (PP), GMFR and 95% CI results are presented in Table 30 (IMM) and Table 31 (PP), seropositivity rates and 95% CIs are presented in Table 32 (IMM) and Table 33 (PP), and seroconversion results and 95% CIs are presented in Table 34 (IMM) and Table 35 (PP). Denominators for percentages will be the number of subjects with non-missing data at

the applicable time point and 95% CI will be calculated using Clopper-Pearson methodology from a binomial distribution.

Graphical presentations of immune response by treatment group and baseline flavivirus immune status will include reverse cumulative distribution curves (Figure 24 through Figure 35) and longitudinal presentation of GMTs (Figure 38 and Figure 39), seropositivity at a threshold of ≥200 (Figure 40 and Figure 41), seropositivity at a threshold of ≥600 (Figure 42 and Figure 43), and percent seroconversion (Figure 44 and Figure 45).

A listing of ZIKV ELISA titers by subject, treatment group, baseline flavivirus immune status, planned time point, and actual study day is presented in Listing 8.

8.3. Exploratory Immunogenicity Analyses

Not applicable.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of sex, ethnicity, race, baseline flavivirus immune status, age, and BMI will be presented by treatment group and overall (Table 17 and Table 18). 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 eCRF as "No" to each racial option.

9.1.1. Pre-Existing Medical Conditions

Pre-existing medical conditions will be summarized by MedDRA System Organ Class, treatment group and overall (Table 19). Individual subject listings will be presented for all demographics in Listing 6.

9.1.2. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by WHO Drug Level 1 and Level 2 Codes, treatment group, and overall (Table 237). Individual subject listings will be presented for all concomitant medications (Listing 22).

9.2. Measurements of Treatment Compliance

All subjects were to receive 2 doses of investigational product administered in the clinic. The number of doses of investigational product administered to subjects will be presented by enrollment group as part of the subject disposition table (Table 11).

A listing of subjects who discontinued dosing and the reason will be included in Listing 2.

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once per AE using the event with maximum severity and any repetitions of adverse events within a subject will be ignored; the denominator will be the total treatment group size or the corresponding number of subjects receiving the second dose, as appropriate. All unsolicited adverse events reported will be included in Listing 11.

An overall summary of adverse events from first administration of study vaccine to the end of the study is presented in Table 36, Table 37, and Table 38 for all subjects, baseline flavivirus positive subjects and baseline flavivirus negative subjects, respectively.

9.3.1. Solicited Events and Symptoms

Statistical comparisons of the frequency and duration of vaccine related Grade 3 local, systemic, or laboratory AE, and Grade 2 or greater local or systemic reactogenicity are presented post dose 1, post dose 2, and post any dose in Table 43, overall and by pre-vaccination flavivirus immune status. Frequencies of each adverse event are compared between dosage groups using Fisher's Exact test. The distribution of the duration of adverse events (excluding laboratory AEs) will be compared between all dosage groups using the 2-samples Wilcoxon rank sum test.

The frequency and proportion of subjects experiencing any local or systemic solicited event over the 8-day post-vaccination reporting period will be summarized by dose number, pre-vaccination flavivirus immune status, severity and treatment group in Table 44 (post dose 1, post dose 2, and post any dose).

The number, percentage, and exact 95% CI of subjects experiencing each solicited event over the 8-day post-vaccination reporting period, collected in-clinic pre-vaccination, post-vaccination and via memory aid, will be summarized by pre-vaccination flavivirus immune status, dose number and symptom in Table 45 (all subjects), Table 46 (baseline ZIKV seropositive subjects), Table 47 (baseline ZIKV seronegative subjects), Table 48 (baseline ZIKV seropositive and DENV seropositive subjects), Table 49 (baseline ZIKV seropositive and DENV seronegative subjects), Table 50 (baseline ZIKV seronegative and DENV seropositive subjects), and Table 51 (baseline ZIKV seronegative and DENV seronegative subjects).

The frequency and proportion of subjects experiencing any mild, moderate, or severe solicited local or systemic reaction will be summarized by pre-vaccination flavivirus immune status, treatment group, dose number and reaction in Table 52 (local; all subjects), Table 53, (local; baseline ZIKV seropositive), Table 54 (local; baseline ZIKV seronegative), Table 55 (local; baseline ZIKV seropositive and DENV seropositive), Table 56 (local; baseline ZIKV seropositive and DENV seronegative), Table 57 (local; baseline ZIKV seronegative and DENV seropositive), Table 58 (local; baseline ZIKV seronegative and DENV seronegative), Table 59 (systemic; all subjects), Table 60, (systemic; baseline ZIKV seropositive), Table 61 (systemic; baseline ZIKV seronegative), Table 62 (systemic; baseline ZIKV seropositive and DENV seropositive), Table 63 (systemic; baseline ZIKV seropositive DENV seronegative),Table 64 (systemic; baseline ZIKV seronegative and DENV seropositive), and Table 65 (systemic; baseline ZIKV seronegative DENV seronegative).

The frequency and proportion of subjects experiencing a mild, moderate, or severe **local or systemic solicited reaction** will be summarized by baseline flavivirus immune status, treatment group, dose number, reaction, pre-dose, and by post-vaccination day in the following tables:

Table A: Severity of Solicited Local or Systemic Reactogenicity Events, by Post-Vaccination Day:

Baseline Flavivirus Immune Status	2.5 mcg ZIPV			5 mcg ZIPV			Placebo		
	Post-Dose 1	Post-Dose 2	Post Any Dose	Post-Dose 1	Post-Dose 2	Post Any Dose	Post-Dose 1	Post-Dose 2	Post Any Dose
All Subjects	Table 66	Table 67	Table 68	Table 69	Table 70	Table 71	Table 72	Table 73	Table 74
Baseline ZIKV Seropositive	Table 75	Table 76	Table 77	Table 78	Table 79	Table 80	Table 81	Table 82	Table 83
Baseline ZIKV Seronegative	Table 84	Table 85	Table 86	Table 87	Table 88	Table 89	Table 90	Table 91	Table 92
Baseline ZIKV Seropositive and DENV Seropositive	Table 93	Table 94	Table 95	Table 96	Table 97	Table 98	Table 99	Table 100	Table 101
Baseline ZIKV Seropositive and DENV Seronegative	Table 102	Table 103	Table 104	Table 105	Table 106	Table 107	Table 108	Table 109	Table 110

Baseline ZIKV Seronegative and DENV Seropositive	Table 111	Table 112	Table 113	Table 114	Table 115	Table 116	Table 117	Table 118	Table 119
Baseline ZIKV Seronegative and DENV Seronegative	Table 120	Table 121	Table 122	Table 123	Table 124	Table 125	Table 126	Table 127	Table 128

Figure 46, Figure 47, and Figure 48 will summarize the solicited local adverse event data overall and by treatment group and display the maximum severity experience by each subject for each solicited event following any dose, post dose 1, and post dose 2, respectively. Similar summaries for solicited systemic events are presented in Figure 49, Figure 50, and Figure 51.

Figure 52, Figure 53, and Figure 54 will summarize the solicited local event data overall and by treatment group and display the maximum severity experienced by each subject pre-dose and each day post-dose, post any dose, post dose 1, and post dose 2, respectively. Figure 55, Figure 56, and Figure 57 are similar summaries for solicited systemic event data.

A listing of systemic and local solicited events is provided in Listing 9 and Listing 10, respectively.

9.3.2. Unsolicited Adverse Events

The frequency of all unsolicited AEs reported per subject from first administration of study vaccine to 28 days after the last vaccination are presented by MedDRA SOC, PT, severity, relationship to study treatment, and baseline flavivirus status in Table 129 (2.5 mcg ZPIV), Table 130 (5 mcg ZPIV), and Table 131 (placebo).

The frequency of all unsolicited AEs reported per subject from first administration of study vaccine to 28 days after the last vaccination are presented in the following tables by MedDRA SOC, PT, severity, dose, and baseline flavivirus status in Table 132 (2.5 mcg ZPIV), Table 133 (5 mcg ZPIV), and Table 134 (placebo).

Figure 58, Figure 59, and Figure 60 are graphical representations of the number and severity of all unsolicited adverse events overall and by treatment group and MedDRA SOC following any dose, post dose 1, and post dose 2, respectively. Similar presentations for adverse events determined to be related to study product are available in Figure 61, Figure 62, and Figure 63.

Refer to Listing 11 for a detailed listing of all unsolicited adverse events. Table 189 includes a listing of all serious adverse events and Table 190 includes a listing of all non-serious unsolicited moderate or severe adverse events.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

Serious adverse events including deaths will be listed in Table 189. A listing of AESIs and NOCMCs will be presented in Table 191.

The number and percentage of subjects reporting new onset chronic medical conditions is summarized by MedDRA SOC and PT by treatment group and baseline flavivirus immune status in Table 135. Similar summaries for the number and percentage of subjects reporting AESIs related to study treatment are presented in Table 136. The duration in days of AESIs is summarized in Table 137.

Summaries of the number of subjects reporting serious adverse events related to study treatment are available in Table 138. The duration in days of the related SAEs is summarized in Table 139.

9.5. Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt was made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A listing of pregnancies and outcomes will be presented (Listing 20, Listing 24, Listing 25, Listing 26, and Listing 27).

9.6. Clinical Laboratory Evaluations

Safety laboratory tests include WBC, hemoglobin, hematocrit and platelets for hematology; ALT, AST, total bilirubin, BUN, and creatinine for chemistry; and urine dipstick for protein and glucose for urinalysis. Table 192 (chemistry), Table 193 (hematology) and Table 194 (urinalysis) are listings of all abnormal laboratory results.

The severity of clinical lab results by frequency and proportion of subjects for chemistry, hematology, and urinalysis clinical laboratory parameters conducted at screening (baseline) and Days 8, 15, 36, 43, and by maximum severity post-baseline are presented overall and by pre-vaccination flavivirus immune status and parameter as listed in Table B below.

The frequency and proportion of subjects with abnormal hematology, chemistry and urinalysis clinical laboratory parameters related to study treatment at each timepoint and by maximum severity post-baseline are presented by pre-vaccination flavivirus immune status and parameter as listed in Table C below.

Descriptive statistics of each hematology and chemistry clinical laboratory parameter at each scheduled time point, including change from baseline statistics, are presented by parameter as listed in Table D below.

Labs may also be performed as necessary at unscheduled visits for follow-up of an adverse event. Figure 64, Figure 65, and Figure 66 display abnormal results by laboratory parameter, severity, and treatment group and includes all values reported after treatment administration (scheduled and supplemental) for chemistry, hematology, and urinalysis labs, respectively. Mean changes from baseline at each scheduled time point for each chemistry and hematology lab are presented by treatment group in Figure 67 through Figure 75. Listing 17, Listing 18, and Listing 19 include listings of chemistry, hematology, and urinalysis results at any time post-treatment administration, respectively.

Table B: Severity of Clinical Lab Results:

Any Chemistry Parameter	Table 195
ALT	Table 196
AST	Table 197
Total Bilirubin	Table 198
BUN	Table 199
Creatinine	Table 200
Any Hematology Parameter	Table 212

WBC	Table 213
Hemoglobin	Table 214
Hematocrit	Table 215
Platelet Count	Table 216
Any Urinalysis Parameter	Table 226
Protein	Table 227
Glucose	Table 228

Table C: Severity of Abnormal Clinical Lab Results Related to Study Treatment

Any Chemistry Parameter	Table 201
ALT	Table 202
AST	Table 203
Total Bilirubin	Table 204
BUN	Table 205
Creatinine	Table 206
Any Hematology Parameter	Table 217
WBC	Table 218
Hemoglobin	Table 219
Hematocrit	Table 220
Platelet Count	Table 221
Any Urinalysis Parameter	Table 229
Protein	Table 230
Glucose	Table 231

Table D: Descriptive Statistics of Chemistry and Hematology Clinical Lab Results

	All Subjects
Chemistry Parameters	
ALT	Table 207
AST	Table 208
Total Bilirubin	Table 209
BUN	Table 210
Creatinine	Table 211
Hematology Parameters	

WBC	Table 222
Hemoglobin	Table 223
Hematocrit	Table 224
Platelet Count	Table 225

9.7. Vital Signs and Physical Evaluations

Vital sign measurements included systolic blood pressure, diastolic blood pressure, pulse, and oral temperature. The frequency and proportion of subjects with abnormal vital signs results is presented by study visit, treatment group and severity in Table 232 (any assessment), Table 233 (oral temperature), Table 234 (pulse), Table 235 (systolic blood pressure) and Table 236 (diastolic blood pressure). Listing 20 includes a listing of vital signs at any time post-treatment administration; physical exam findings are presented in Listing 21.

9.8. Concomitant Medications

Concomitant medications will be summarized in Table 237 by WHO ATC Code Levels 1 and 2 and by treatment group. A listing of concomitant medications is presented in Listing 22.

9.9. Other Safety Measures

Summary tables of acute febrile illness (AFI) and acute rash illness (ARI) events will be presented. The percentage of subjects who develop ARI or AFI will be summarized by treatment group and baseline flavivirus status. Additionally, summary tables for AFI/ARI events will be presented by baseline flavivirus status.

Summaries of subjects reporting any events, any medically treated events, and any events requiring concomitant medication, including the total number of events and the number, percentage and exact 95% Clopper-Pearson CI of subjects reporting an event, will be presented for all subjects and by baseline flavivirus immune status in Table 140, Table 141, Table 142, Table 143, and Table 144. Similar summaries presented by infection confirmation method are presented in Table 147, Table 148, Table 149, Table 150 and Table 151.

Summaries of laboratory confirmed ZIKV and DENV infections are also presented. ZIKV and DENV infection is presented via two methods: subjects presenting with ARI/AFI and positive Arbovirus PCR result within 14 days of symptom onset or subjects presenting with ARI/AFI and a 4-fold rise in ZIKV or DENV titers following the onset of illness compared to prior to illness. The total number of laboratory confirmed ZIKV or DENV infections are summarized by treatment group, baseline flavivirus status, and confirmation method in Table 154, Table 155, Table 156, Table 157, and Table 158.

The distribution of the maximum severity of symptoms of each ARI/AFI event by baseline flavivirus status and treatment group will be presented in Table 161, Table 162, Table 163, Table 164, and Table 165, as well as by infection confirmation status in Table 168, Table 169, Table 170, Table 171, and Table 172. For subjects reporting at least one AFI/ARI the duration of reported symptoms will be described in Table 175, Table 176, Table 177, Table 178, Table 179, and by infection confirmation status in Table 182, Table 183, Table 184, Table 185, and Table 186.

Individual subject listings of AFI/ARI data will be included in Listing 12 (subject information), Listing 13 (medical treatment sought for ARI/AFI), Listing 14 (ARI/AFI symptoms), Listing 15 (vital signs), and Listing 16 (laboratory results).

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

See Section 8.

12. OTHER ANALYSES

Not applicable.

13. 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" The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The study enrollment plan was modified in protocol amendment 5.0 (18 December 2018) to address the loss of evaluable subjects in Group 1 and delay of enrollment due to Hurricane Maria. The original study design planned to enroll 40 ZPIV recipients and 5 placebo recipients in each Group. Due to Hurricane Maria, 11 subjects enrolled in Group 1 had loss of samples at key timepoints. To rebalance the number of evaluable subjects between Groups, Group 1 enrollment was increased by 5 subjects and Group 2 enrollment was decreased by 5 subjects, for a total enrollment of 50 subjects in Group 1 and 40 in Group 2. Treatment assignments for both groups are assigned according to the originally planned 8:1 ratio of ZPIV:placebo.

The data summaries described for the second and third interim analyses were combined into a single interim analysis. Therefore, only two interim analyses were actually performed prior to final database lock and the clinical study report.

Baseline flavivirus screening was expanded from testing for ZIKV and DENV antibodies to testing for antibodies to 4 flaviviruses: ZIKV, DENV, YFV, and WNV. Results of baseline YFV and WNV testing will not be used in analysis for the CSR.

The second exploratory endpoint was modified in protocol version 6.0 (06 December 2021) to clarify how ZIKV and DENV infection would be confirmed in subjects reporting AFI/ARI. The timepoints were adjusted to run ZIKV and DENV MN50 on samples immediately before and immediately following the illness visit(s) wherever possible.

16. REFERENCES

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 1: Schematic of Study Design

Dosage Group	Approximate # of Subjects (8:1 ratio)	Treatment at Days 1 and 29
Group 1 Sentinels	2	5 mcg ZPIV
Group 1 Non-Sentinels	43	5 mcg ZPIV
	5	Placebo
Group 2	35	2.5 mcg ZPIV
	5	Placebo

Table 2: Schedule of Study Procedures

Study Visit	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**Fever/ Rash**	**Early Term**	**Unsch Visit**
Overall Study Day	Screen D-28 to--1	D1 Vaccination	D2	D4 +1 Phone call	D8 ±1	D15 ±1	D29 ±3	D30	D32 +1 Phone call	D36 ±1	D43 ±2	D57 ±3	D107 ± 14 Phone call	D157±14 Phone call	D209 ±14	D268 ±14 Phone Call	D328 ±14 Phone call	D388 ±14			
Study Day after Second Vaccination							D1 Vaccination 2	D2	D4+1 Phone call	D8 ±1	D15 ±2	D29 ±3	D79±14 Phone call	D129±14 Phone call	D181 ±14	D240±14 Phone call	D300 ±14 Phone call	D360 ±14			
Informed Consent[1]	X																				
Review Eligibility	X	X					X														
Medical History[3]	X	X[2]	X	X	X	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (T,P,& BP)[5]	X	X	X		X	X	X	X		X	X	X							X	X[15]	X[15]
Height & Weight	X																				
Abbreviated Physical Exam[6]	X																				
Serology (HIV-1/2, HBV, HCV)	X																				
Serology (ZIKV, DENV)	X																		X[19]		
Randomization/ Enrollment		X																			
Evaluate Pre-administration reactogenicity		X					X														
Study Product Administration and observation for 30 minutes		X					X														

Table 2: Schedule of Study Procedures (*continued)*

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	V13	V14	V15	V16	V17	Fever/ Rash	Early Term	Unsch Visit
Give Memory Aid[9]		X					X														
Evaluate vaccine site[11]		X	X		X	X	X	X		X	X	X								X[13]	X[13]
Targeted Physical Exam[6]		X	X		X	X	X	X		X	X	X			X			X	X	X	X
Serum or Urine Pregnancy Test[7]	X	X					X					X								X[13]	X[13]
Safety Lab Evaluations[8]	X				X	X				X	X									X[14]	X[14]
Urine for protein and glucose	X				X	X				X	X									X[14]	X[14]
Concomitant Medications	X	X	X	X	X	X	X[2]	X	X	X	X	X							X	X	X
Review Memory Aid			X	X	X			X	X	X										X[12]	X[12]
AE Collection		X	X	X	X	X	X	X	X	X	X	X							X	X[15]	X[15]
AFI/ARI/ SAE/AESI/new medical conditions[22, 20]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum for Humoral Immunity		X[16]				X	X[16]				X	X			X			X		X[17]	X[17]
CPT tubes for future immunity/systems biology[21]		X[16,18,]	X[18]		X[18]	X[18]	X[16,18]	X[18]		X[18]	X[18]	X			X			X		X[17]	X[17]
Paxgene tubes for future systems biology		X[16]	X		X	X	X[16]	X		X	X									X[17]	X[17]
AFI/ARI /SAE/AESI/new medical conditions[22, 20]	X	X	X	X	X	X															
Medical History[3]	X	X	X	X	X	X															

Table 2: Schedule of Study Procedures (*continued)*

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	V13	V14	V15	V16	V17	Fever/ Rash	Early Term	Unsch Visit
Serum for Humoral Immunity			X			X															
CPT tubes for future immunity/systems biology			X			X															
Targeted Physical exam[6]			X			X															

Table 2: Schedule of Study Procedures (*continued)*

Study Visit	V00	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11	V12	V13	V14	V15	V16	V17	Fever/ Rash	Early Term	Unsch Visit

Definitions: AE = adverse event; BP = blood pressure; DENV = dengue virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV 1/2 = human immunodeficiency virus types 1 and 2; HR = heart rate; T = body temperature; SAE = serious adverse event; AESI = Adverse event of Special Interest; ZIKV = Zika virus.

[1] Must describe study, administer informed consent, and have informed consent form (ICF) signed prior to initiation of any study-related procedures.

[2] Subjects must meet eligibility criteria; these criteria should be reviewed prior to administration of prime and boost dose of study vaccine or placebo.

[3] Obtain complete medical history from subject at first screening visit and update it at Day 1 prior to vaccination; interim medical history obtained at follow-up visits.

[5] Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. Repeat of vital signs allowed once if found to be abnormal on Day 1 and Day 29.

[6] Abbreviated physical examination is a complete exam with no genitourinary and rectal exam performed. Targeted physical exams are done at scheduled clinic visits if indicated based on review of medical history.

[7] Females of childbearing potential will have serum pregnancy test done at screening and urine pregnancy test done in the 24 hours prior to each study vaccination; Results must be negative to enroll subject and negative prior to each study vaccination. Urine pregnancy test may be done if subject withdrawals from study early or has an unscheduled visit.

[8] Screening laboratory tests, including WBC, hemoglobin, hematocrit, platelet count, ALT, AST, bilirubin, BUN, and creatinine, may be repeated once on a second screening visit If test is out of acceptable range, provided there is an alternative explanation for the out of range value; All screening tests need to be done within 28 days of Day 1, otherwise all tests, except for serology for HIV 1/2, Hepatitis C virus, or Hepatitis B surface antigen, will need to be repeated within the screening period. Safety laboratories include WBC, hemoglobin, hematocrit, platelet count, ALT, AST, bilirubin, BUN, and creatinine.

[9] Distribute memory aid to subjects and give them study materials.

[11] Assess vaccination site.

[12] If visit occurs $\leq$8 days after 1st of 2nd vaccination. Includes local and systemic reactogenicity assessment

[13] If prior to $\leq$28 days after the last study vaccination.

[14] If visit occurs $\leq$15 days after 1st or 2nd vaccination.

[15] If visit occurs on or prior to Day 57.

[16] Obtained prior to vaccination.

[17] If visit occurs within window of a study Day when these labs would be collected.

[18] Part of the plasma from the CPT tubes will be saved for systems biology.

[19] Baseline serology will include testing for DENV and ZIKV. AFI/ARI assessment will include testing for DENV, ZIKV, and CHIKV.

Table 3: Local (Injection Site) Reactogenicity and Measurement

Reactogenicity	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Local reactions			
Pain	Does not interfere with activity **and** no pain medication is taken	Repeated use of non-narcotic pain reliever >24 hours **or** interferes with activity	Any use of narcotic pain reliever **or** prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement **and** it interferes with daily activity	Significant discomfort at rest **and** it prevents daily activity
Pruritis (itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (bruising)[a]	25-50 mm	51-100 mm	>100 mm
Erythema (redness)[a]	25-50 mm	51-100 mm	>100 mm
Induration (hardness)/swelling[b]	25-50 mm **and** does not interfere with activity	51-100 mm **or** interferes with activity	>100 mm **or** prevents daily activity

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable. The size of erythema, ecchymosis, and induration/swelling by itself will not be used as halting criteria.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Table 4: Subjective Systemic Reactogenicity Grading

Systemic	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating) Fatigue (Tiredness) Malaise (General Unwell Feeling) Myalgia (Body Aches/Muscular Pain)* Arthralgia (Joint Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache		Some interference with daily activity or it requires > 24 hours of use of non-narcotic pain medication	Significant interference, prevents daily activity or it requires any use of narcotic pain medication
Nausea Vomiting Diarrhea Abdominal Pain Rash*		Some interference with daily activity	Significant interference, prevents daily activity
* Not at injection site.			

Table 5: Quantitative Systemic Reactogenicity Grading

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever[#] - oral[†]	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	>38.9°C >102.0°F
Oral temperature assessed on Day 1 prior to the first study vaccination will be considered as baseline. [#] A fever can be considered not related to the study vaccine if an alternative etiology can be documented. † Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature			

Table 6: Vital Sign Adverse Event Grading Scale

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bradycardia - beats per minute	50 – 54 (or 45 – 49 if baseline < 60)	45 – 49 (or 40 – 44 if baseline < 60)	<45 (or <40 if baseline < 60)
Tachycardia - beats per minute	101 – 115	116 – 130	>130 (or ventricular dysrhythmias)
Hypotension (systolic) mm Hg	85 – 89	80 – 84	<80
Hypotension (diastolic) mm Hg	50 – 54	45 – 49	<45
Hypertension (systolic) mm Hg	141 – 150	151 – 160	>160
Hypertension (diastolic) mm Hg	91 – 95	96 – 100	>100
#Pulse and blood pressure assessed at screening will be considered as baseline.			

Table 7: Laboratory Adverse Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hematology			
WBC 10^3/UL (Decrease)	2.5 – 3.4	1.5 – 2.4	<1.5
WBC 10^3/UL (Increase)	10.9– 15.0	15.1 – 20.0	>20.0
HgB g/dL Female	10.5-11.4	8.5-10.4	<8.5
HgB g/dL Male	12.0-13.4	10.0-11.9	<10.0
HCT % decrease Female	31.5-34.2	25.5-31.4	<25.5
HCT % decrease Male	36.0-40.2	30-35.9	<30
HCT % increase	1.01-1.1 X ULN	1.11-1.2 X ULN	>1.2 X ULN
Platelets cell/10^3/UL (Decrease)	100-149	99-75	<75
Chemistry			
ALT	1.25 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 x ULN
AST	1.25 – 3.0 x ULN	>3.0 – 5.0 x ULN	> 5.0 x ULN
Bilirubin– when ALT $\geq$3 x ULN	1.25 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 x ULN
Bilirubin	1.25 – 2.0 x ULN	>2.0 – 2.5 x ULN	>2.5 x ULN
BUN mg/dL	26-30	31-35	> 35
Creatinine mg/dL	1.1 – 1.7	1.8 – 2.0	>2.0
Urine Dipstick			
Protein	1+	2+	>2+
Glucose	1+	2+	>2+

Table 8: Probability of Observing at Least One Adverse Event Given Various True Event Rates

Sample Size	"True" Unknown Event Rate	Probability of Observing an Event (%)	Sample Size	"True" Unknown Event Rate	Probability of Observing an Event (%)
35	0.1%	3.4	80	0.1%	7.7
	0.5%	16.1		0.5%	33.0
	1.0%	29.7		1.0%	55.2
	2.0%	50.7		2.0%	80.1
	3.0%	65.6		3.0%	91.3
	4.0%	76		4.0%	96.2
	5.0%	83.4		5.0%	98.3
	10.0%	97.5		10.0%	>99.9
	20.0%	>99.9		20.0%	>99.9

Table 9: Minimum Detectable Event Rates given various levels of Power

Sample Size	Desired Power Level	Detectable Event Rate	Sample Size	Desired Power Level	Detectable Event Rate
35	0.80	4.5%	80	0.80	2.0%
	0.90	6.4%		0.90	2.8%
	0.95	8.2%		0.95	3.7%
	0.99	12.3%		0.99	5.6%

Table 10: Distribution of Protocol Deviations by Category, Type, and Treatment Group, All Enrolled Subjects

[Implementation note: the table will only include the deviation categories and types that occurred.]

Category	Deviation Type	2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Any category	Any type	x	x	x	x	x	x	x	x
Eligibility/ enrollment	Any type	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x
	Met exclusion criterion								
	ICF not signed prior to study procedures								
	Other								
Treatment administration schedule	Any type								
	Out of window visit								
	Missed visit/visit not conducted								
	Missed treatment administration								
	Delayed treatment administration								
	Other								
Follow-up visit schedule	Any type								
	Out of window visit								
	Missed visit/visit not conducted								
	Other								
Protocol procedure/ assessment	Any type								
	Incorrect version of ICF signed								
	Blood not collected								
	Other specimen not collected								
	Too few aliquots obtained								
	Specimen result not obtained								

Table 10: Distribution of Protocol Deviations by Category, Type, and Treatment Group, All Enrolled Subjects (*continued)*

Category	Deviation Type	2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
	Required procedure not conducted								
	Required procedure done incorrectly								
	Study product temperature excursion								
	Specimen temperature excursion								
	Other								
Treatment administration	Any type								
	Required procedure done incorrectly								
	Study product temperature excursion								
	Other								
Blinding policy/ procedure	Any type								
	Treatment unblinded								
	Other								
N=Number of subjects enrolled									

14.1.1 Disposition of Subjects

Table 11: Subject Disposition by Treatment Group

Subject Disposition	2.5 mcg ZPIV	5 mcg ZPIV	Placebo	All Subjects
	n (%)	n (%)	n (%)	n (%)
Screened	N/A	N/A	N/A	xxx
Enrolled/Randomized	xx	xx	xx	xx
Received Vaccination 1	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Received Vaccination 2				
Received All Scheduled Treatments [a]				
Discontinued Dosing [b]				
Terminated from Study Follow-Up [b]				
Completed Follow-Up [b]				
Completed Study Per Protocol [b, c]				

Denominators for percentages are the numbers of subjects enrolled/randomized unless otherwise specified.

[a] Refer to Appendix 16.2.1 for reasons subjects discontinued treatment or terminated early.

[b] Out of all randomized and vaccinated subjects.

[c] Refer to Appendix 16.2.3 for reasons subjects were excluded from the Per Protocol population.

Table 12: Early Withdrawals and Treatment Discontinuations by Treatment Group – All Enrolled and Randomized Subjects

Subject Disposition	2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	p-value[a]
	n (%)	n (%)	n (%)	
All Subjects Enrolled				
Total number of subjects[b]	x	X	x	N/A
Withdrew from Study	x (xx)	x (xx)	x (xx)	x.xxx
Discontinuation of Study Vaccination	x (xx)	x (xx)	x (xx)	x.xxx
Baseline ZIKV Seropositive				
Total number of subjects[b]				
Withdrew from Study				
Discontinuation of Study Vaccination				
Repeat for:				
Baseline ZIKV Seronegative				
Baseline ZIKV Seropositive and DENV Seropositive				
Baseline ZIKV Seropositive and DENV Seronegative				
Baseline ZIKV Seronegative and DENV Seropositive				
Baseline ZIKV Seronegative and DENV Seronegative				

N = Number of subjects enrolled

[a] Fisher's exact 2-tailed test of the homogeneity and independence of withdrawals or discontinuations between the 3 treatment groups.

[b] Used as denominator for percentages.

Table 13: Analysis Populations by Treatment Group

[Implementation note: For visit-specific PP population exclusions, include only the reasons for which at least one subject is excluded.]

		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
Analysis Populations	**Reason Subjects Excluded**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Safety Population	Did not receive at least one study vaccination								
Immunogenicity Population	Does not have pre- and at least one post-study vaccination samples for immunogenicity testing for which valid results were reported.								
	Loss of samples at pre-vaccination timepoints due to natural disaster[a]								
Per Protocol Population	**Any Time Point**								
	Any Reason								
	Found to be ineligible at baseline								
	Second vaccination not received[b]								
	Second vaccination received out of window[b]								
	Receipt of non-study licensed live vaccine within 30 days prior to or after study vaccination[b]								
	Receipt of non-study licensed inactivated vaccine within 14 days prior to or after study vaccination[b]								
	Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after study vaccination[b]								
	The visit occurred substantially out of window								
	Other major protocol deviation deemed exclusionary by study team								
	Prior to or at Day 1 visit (Visit 01):								
	Any Reason								
	Receipt of non-study licensed live vaccine within 30 days prior to or after study vaccination[b]								
	Receipt of non-study licensed inactivated vaccine within 14 days prior to or after study vaccination[b]								
	Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after study vaccination[b]								

Table 13: Analysis Populations by Treatment Group *(continued)*

		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
Analysis Populations	**Reason Subjects Excluded**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	Other major protocol deviation deemed exclusionary by study team								
	Prior to or at Day 15 visit (Visit 05):								
	Any Reason								
	Receipt of non-study licensed live vaccine within 30 days prior to or after study vaccination[b]								
	Receipt of non-study licensed inactivated vaccine within 14 days prior to or after study vaccination[b]								
	Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after study vaccination[b]								
	The visit occurred substantially out of window								
	Other major protocol deviation deemed exclusionary by study team								
	Prior to or at Day 29 visit (Visit 06):								
	Any Reason								
	Second vaccination not received[b]								
	Second vaccination received out of window[b]								
	Receipt of non-study licensed live vaccine within 30 days prior to or after study vaccination[b]								
	Receipt of non-study licensed inactivated vaccine within 14 days prior to or after study vaccination[b]								
	Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days prior to or after study vaccination[b]								
	The visit occurred substantially out of window								
	Other major protocol deviation deemed exclusionary by study team								
	Repeat Day 29 for:								
	Prior to or at Day 43 visit (Visit 10):								
	Prior to or at Day 57 visit (Visit 11):								

Table 13: Analysis Populations by Treatment Group *(continued)*

		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
Analysis Populations	**Reason Subjects Excluded**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	Prior to or at Day 290 visit (Visit 14):								
	Prior to or at Day 388 visit (Visit 17):								
	Prior to or at Day 569 visit (Visit 20):								
	Prior to or at Day 750 visit (Visit 23):								

N=Total number of subjects enrolled.

Subjects may be excluded from an analysis population for multiple reasons.

[a] Subjects are excluded only from immunogenicity analyses which use pre-vaccination titers, e.g., GMFR

[b] Subjects are excluded from per protocol analyses at all timepoints subsequent to the occurrence of this protocol deviation. All instances of exclusion are summarized in this table. Subject data collected up to the time the exclusionary criterion is met is eligible for analysis.

Table 14: Number of Subjects in Immunogenicity and Per Protocol Populations with Data Available by Analysis Type, Time Point, and Treatment Group

Analysis Population	Treatment Group	Baseline		Day 15		Day 29 (Pre-Dose 2)		Day 43 (14 Days Post-Dose 2)		Day 57 (28 Days Post-Dose 2)		Day 209 (180 Days Post-Dose 2)		Day 388 (359 Days Post-Dose 2)		Day 569 (540 Days Post-Dose 2)		Day 750 (721 Days Post-Dose 2)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Geometric Mean Titer & Seropositivity																			
Immunogenicity	2.5 mcg																		
	5 mcg																		
	Placebo																		
Per Protocol	2.5 mcg																		
	5 mcg																		
	Placebo																		
Geometric Mean Fold Rise[a] and Seroconversion[a]																			
Immunogenicity	2.5 mcg																		
	5 mcg																		
	Placebo																		
Per Protocol	2.5 mcg																		
	5 mcg																		
	Placebo																		

[a] For time points following baseline, the subject must also have baseline measurements to be counted in this table.

Table 15: Date of First Treatment by Treatment Group

[Implementation Note: dates could be grouped by calendar month, bi-weekly or weekly, depending on the distribution.]

Date of Dosing	2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	All Subjects (N=X)
[date 1]	x	x	x	x
[date 2]				
[date 3]				
[date 4]				
[Etc.]				

Table 16: Ineligibility Summary of Screen Failures

[Implementation note: final table will only include criteria where n > 0]

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion		100
Inclusion	Any inclusion criterion		
	[Criterion 1]		
	[Criterion 2]		
	[Criterion 3]		
	[Etc.]		
Exclusion	Any exclusion criterion		
	[Criterion 1]		
	[Criterion 2]		
	[Etc.]		

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

14.1.2 Demographic Data by Study Group

Table 17: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group

Variable	Characteristic	2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx
	Female								
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino								
	Not Reported								
	Unknown								
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	X	xx
	Asian								
	Native Hawaiian or Other Pacific Islander								
	Black or African American								
	White								
	Multi-Racial								
	Unknown								
Baseline Flavivirus Immune Status	Baseline ZIKV Seropositive	x	xx	x	xx	x	xx	x	xx
	Baseline ZIKV Seronegative								
	Baseline ZIKV Seropositive and DENV Seropositive								
	Baseline ZIKV Seropositive and DENV Seronegative								
	Baseline ZIKV Seronegative and DENV Seropositive								
	Baseline ZIKV Seronegative and DENV Seronegative								
N= Number of subjects in the Safety population									

Table 18: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group – Safety Population

Variable	Statistic	2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	All Subjects (N=X)
Age (years)	Mean	xx			
	Standard Deviation	xx.x			
	Median	xx.x			
	Minimum	xx			
	Maximum	xx			
BMI (kg/m^2)[a]	Mean	xx			
	Standard Deviation	xx.x			
	Median	xx.x			
	Minimum	xx			
	Maximum	xx			

N=Number of subjects in the Safety population
[a] at screening

14.1.3 Prior and Concurrent Medical Conditions

Table 19: Summary of Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

	2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
Any SOC	x	xx	x	xx	x	xx	X	xx
[SOC 1] [SOC 2]								
[SOC 3]								
[Etc.]								
N=Number of subjects in the Safety population. Pre-existing medical conditions defined as any condition occurring prior to enrollment.								

14.2 Immunogenicity Data

ZIKV Microneutralization Titers

Table 20: ZIKV Microneutralization Antibody (MN50) Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

[Implementation note: If a baseline flavivirus subgroup includes fewer than 2 subjects, the GMT and 95% CI fields will be populated with 'N/A'.]

Time Point	Baseline Flavivirus Immune Status	2.5 mcg ZPIV			5 mcg ZPIV			Placebo		
		n	GMT	95% CI	n	GMT	95% CI	n	GMT	95% CI
Baseline	All Subjects	x	xx	xx.x, xx.x	x	xx	xx.x, xx.x	x	xx	xx.x, xx.x
	Baseline ZIKV Seropositive									
	Baseline ZIKV Seronegative									
	Baseline ZIKV Seropositive and DENV Seropositive									
	Baseline ZIKV Seropositive and DENV Seronegative									
	Baseline ZIKV Seronegative and DENV Seropositive									
	Baseline ZIKV Seronegative and DENV Seronegative									
Repeat Baseline for:										
Day 29 (Pre-Dose 2)										
Day 57 (28 Days Post-Dose 2)										
Day 209 (180 Days Post-Dose 2)										
Day 750 (721 Days Post-Dose 2)										
Peak Post-Baseline										

n = Number of subjects in the immunogenicity population with non-missing immunogenicity data at the specified time point.
95% CI = 95% confidence interval based on Student's t-distribution.

Table 21: ZIKV Microneutralization Antibody (MN50) Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

Table 22: ZIKV Microneutralization Antibody (MN50) Geometric Mean Fold Rise (GMFR) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

[Implementation note: baseline results are not included in this table.]

Table 23: ZIKV Microneutralization Antibody (MN50) Geometric Mean Fold Rise (GMFR) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

[Implementation note: baseline results are not included in this table.]

Table 24: ZIKV Microneutralization Antibody (MN50) Seropositivity Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

[Implementation note: If a baseline flavivirus subgroup includes fewer than 2 subjects, the % and 95% CI fields will be populated with 'N/A'.]

Time Point	Outcome	Baseline Flavivirus Immune Status	2.5 mcg ZPIV				5 mcg ZPIV				Placebo			
			N*	n	%	95% CI	N*	n	%	95% CI	N*	n	%	95% CI
Baseline	Titer ≥10	All Subjects												
		Baseline ZIKV Seropositive												
		Baseline ZIKV Seronegative												
		Baseline ZIKV Seropositive and DENV Seropositive												
		Baseline ZIKV Seropositive and DENV Seronegative												
		Baseline ZIKV Seronegative and DENV Seropositive												
		Baseline ZIKV Seronegative and DENV Seronegative												
	Titer ≥100	All Subjects												
		Baseline ZIKV Seropositive												
		Baseline ZIKV Seronegative												
		Baseline ZIKV Seropositive and DENV Seropositive												
		Baseline ZIKV Seropositive and DENV Seronegative												
		Baseline ZIKV Seronegative and DENV Seropositive												
		Baseline ZIKV Seronegative and DENV Seronegative												
Repeat Baseline for:														
Day 29 (Pre-Dose 2)														

Table 24: ZIKV Microneutralization Antibody (MN50) Seropositivity Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status -- Immunogenicity Population *(continued)*

Day 57 (28 Days Post-Dose 2)														
Day 209 (180 Days Post-Dose 2)														
Day 750 (721 Days Post-Dose 2)														
Peak Post-Baseline														

N* = Number of subjects with results available at the specified time point

n = number of subjects seropositive at the specified time point

95% CI = Exact 95% Clopper-Pearson confidence interval.

Table with similar format:

Table 25: ZIKV Microneutralization Antibody (MN50) Seropositivity Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

Table 26: ZIKV Microneutralization Antibody (MN50) Seroconversion Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

[Implementation note: If a baseline flavivirus subgroup includes fewer than 2 subjects, the % and 95% CI fields will be populated with 'N/A'.]

Time Point	Baseline Flavivirus Immune Status	2.5 mcg ZPIV				5 mcg ZPIV				Placebo			
		N*	n	%	95% CI	N*	n	%	95% CI	N*	n	%	95% CI
Day 29 (Pre-Dose 2)	All Subjects												
	Baseline ZIKV Seropositive												
	Baseline ZIKV Seronegative												
	Baseline ZIKV Seropositive and DENV Seropositive												
	Baseline ZIKV Seropositive and DENV Seronegative												
	Baseline ZIKV Seronegative and DENV Seropositive												
	Baseline ZIKV Seronegative and DENV Seronegative												
Repeat Day 29 for:													
Day 57 (28 Days Post-Dose 2)													
Day 209 (180 Days Post-Dose 2)													
Day 750 (721 Days Post-Dose 2)													
Peak Post-Baseline													

Table 26: ZIKV Microneutralization Antibody (MN50) Seroconversion Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status -- Immunogenicity Population *(continued)*

Seroconversion is defined as at least a 4-fold rise in ZIKV MN50 titers from baseline.
N* = Number of subjects with results available at baseline and the specified time point
n = number of subjects seroconverting at the specified time point
95% CI = 95% confidence interval.

Table with similar format:

Table 27: ZIKV Microneutralization Antibody (MN50) Seroconversion Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

ZIKV ELISA Titers

Tables with format similar to Table 20:

Table 28: ZIKV ELISA Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

Table 29: ZIKV ELISA Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

Table 30: ZIKV ELISA Geometric Mean Fold Rise (GMFR) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

[Implementation Note: Baseline results are not included in this table.]

Table 31: ZIKV ELISA Geometric Mean Fold Rise (GMFR) Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

[Implementation Note: Baseline results are not included in this table.]

Tables with format similar to Table 24:

Table 32: ZIKV ELISA Seropositivity Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

[Implementation note: seropositivity is defined as titers ≥ 200 and ≥ 600.]

Table 33: ZIKV ELISA Seropositivity Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

[Implementation note: seropositivity is defined as titers ≥ 200 and ≥ 600.]

Tables with format similar to Table 26:

Table 34: ZIKV ELISA Seroconversion Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Immunogenicity Population

Table 35: ZIKV ELISA Seroconversion Results with 95% Confidence Intervals by Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Per Protocol Population

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 36: Overall Summary of Adverse Events – All Subjects

		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
Event Category[a]	**Subcategory**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At least one local solicited adverse event [b]		xx (xx)	xx.x, xx.x	xx (xx)	xx.x, xx.x	xx (xx)	xx.x, xx.x	xx (xx)	xx.x, xx.x
At least one systemic solicited adverse event [b]									
At least one unsolicited adverse event [c]									
At least one related unsolicited adverse event [c]	Any Severity								
	Mild (Grade 1)								
	Moderate (Grade 2)								
	Severe (Grade 3)								
At least one related laboratory adverse event [c]	Any Severity								
	Mild (Grade 1)								
	Moderate (Grade 2)								
	Severe (Grade 3)								
At least one related unsolicited or laboratory adverse event [c]	Any Severity								
	Mild (Grade 1)								
	Moderate (Grade 2)								
	Severe (Grade 3)								
At least one severe (Grade 3) unsolicited adverse event [c]	Any Relationship								
	Related								
	Unrelated								
At least one serious adverse event [d]									
At least one related serious adverse event [d]									
At least one adverse event leading to early termination from the study [d]									

Table 36: Overall Summary of Adverse Events -- All Subjects *(continued)*

		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
Event Category[a]	**Subcategory**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At least one adverse event leading to discontinuation of study product									
At least one adverse event of special interest (AESI) [d]									
At least one related AESI [d]									
At least one new onset chronic medical condition (NOCMC) [d]									
At least one related NOCMC [d]									

N = Number of subjects in the safety population. CI = Exact (Clopper-Pearson) confidence interval.

n = Number of subjects experiencing the event.

[a] Subjects are counted once for each category regardless of the number of events.
[b] Solicited AEs are collected through Day 8 post each dose.
[c] Non-serious unsolicited AEs within 28 days of either dose.
[d] At any time during the study.

Tables with similar format:

Table 37: Overall Summary of Adverse Events – Baseline ZIKV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with specified baseline flavivirus immune status]

Table 38: Overall Summary of Adverse Events – Baseline ZIKV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with specified baseline flavivirus immune status]

Table 39: Overall Summary of Adverse Events – Baseline ZIKV Seropositive and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with specified baseline flavivirus immune status]

Table 40: Overall Summary of Adverse Events – Baseline ZIKV Seropositive and DENV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with specified baseline flavivirus immune status]

Table 41: Overall Summary of Adverse Events – Baseline ZIKV Seronegative and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with specified baseline flavivirus immune status]

Table 42: Overall Summary of Adverse Events – Baseline ZIKV Seronegative and DENV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with specified baseline flavivirus immune status]

14.3.1.1 Solicited Adverse Events

Table 43: Comparison of the Frequency, Type and Duration of Vaccine-Related Grade 3 Local, Systemic or Laboratory AEs and Grade 2 or Greater Local or Systemic Reactogenicity Through Day 8 Post Vaccination

			2.5 mcg ZPIV		5 mcg ZPIV		Placebo		p-value	
Post Dose Number	**AE Type**	**Symptom/Lab AE**	**n**	**Median Duration (Days)**	**n**	**Median Duration (Days)**	**n**	**Median Duration (Days)**	**[a]Frequency**	**[b]Duration**
All Subjects										
Post Dose 1	Number of Subjects in the Safety Population Who Received the Specified Dose		x	N/A	x	N/A	x	N/A	N/A	N/A
	Vaccine related Grade 3 local, systemic or laboratory AE	[Event 1]	x	x.x	x	x.x	x	x.x	x.xxx	x.xxx
		[Event 2]							x.xxx	x.xxx
		[Event 3]							x.xxx	x.xxx
		Etc.							x.xxx	x.xxx
	[*]Grade 2 or greater local or systemic reactogenicity	[Event 1]							x.xxx	x.xxx
		[Event 2]							x.xxx	x.xxx
		[Event 3]							x.xxx	x.xxx
		Etc.							x.xxx	x.xxx
Repeat Post Dose 1 for:										
Baseline ZIKV Seropositive										
Baseline ZIKV Seronegative										
Baseline ZIKV Seropositive and DENV Seropositive										
Baseline ZIKV Seropositive and DENV Seronegative										
Baseline ZIKV Seronegative and DENV Seropositive										
Baseline ZIKV Seronegative and DENV Seronegative										
All Subjects										
Post Dose 2	Number of Subjects in the Safety Population Who Received the Specified Dose		x	N/A	x	N/A	x	N/A	N/A	N/A
		[Event 1]	x	x.x	x	x.x	x	x.x	x.xxx	x.xxx

Table 43: Comparison of the Frequency, Type and Duration of Vaccine-Related Grade 3 Local, Systemic or Laboratory AEs and Grade 2 or Greater Local or Systemic Reactogenicity Through Day 8 Post Vaccination *(continued)*

	Vaccine related Grade 3 local, systemic or laboratory AE	[Event 2]							x.xxx	x.xxx
		[Event 3]							x.xxx	x.xxx
		Etc.							x.xxx	x.xxx
	*Grade 2 or greater local or systemic reactogenicity	[Event 1]							x.xxx	x.xxx
		[Event 2]							x.xxx	x.xxx
		[Event 3]							x.xxx	x.xxx
		Etc.							x.xxx	x.xxx
Repeat Post Dose 2 for:										
Baseline ZIKV Seropositive										
Baseline ZIKV Seronegative										
Baseline ZIKV Seropositive and DENV Seropositive										
Baseline ZIKV Seropositive and DENV Seronegative										
Baseline ZIKV Seronegative and DENV Seropositive										
Baseline ZIKV Seronegative and DENV Seronegative										
All Subjects										
Post Any Dose	Number of Subjects in the Safety Population		x	N/A	x	N/A	x	N/A	N/A	N/A
	Vaccine related Grade 3 local, systemic or laboratory AE	[Event 1]	x	x.x	x	x.x	x	x.x	x.xxx	x.xxx
		[Event 2]							x.xxx	x.xxx
		[Event 3]							x.xxx	x.xxx
		Etc.							x.xxx	x.xxx
	*Grade 2 or greater local or systemic reactogenicity	[Event 1]							x.xxx	x.xxx
		[Event 2]							x.xxx	x.xxx
		[Event 3]							x.xxx	x.xxx
		Etc.							x.xxx	x.xxx
Repeat Post Any Dose for:										

Table 43: Comparison of the Frequency, Type and Duration of Vaccine-Related Grade 3 Local, Systemic or Laboratory AEs and Grade 2 or Greater Local or Systemic Reactogenicity Through Day 8 Post Vaccination *(continued)*

Baseline ZIKV Seropositive
Baseline ZIKV Seronegative
Baseline ZIKV Seropositive and DENV Seropositive
Baseline ZIKV Seropositive and DENV Seronegative
Baseline ZIKV Seronegative and DENV Seropositive
Baseline ZIKV Seronegative and DENV Seronegative
n = Number of subjects [*] Through Day 8 post vaccination [a] Frequencies of adverse events compared between ZPIV dosage groups using Fisher's Exact test. [b] Distribution of the duration of adverse events compared between ZPIV dosage groups using Wilcoxon 2-sample test. Only the frequency, not the duration of laboratory AEs will be compared.

Table 44: Number and Percentage of Subjects Experiencing Any Local or Systemic Solicited Events through Day 8 Post Vaccination by Dose, Baseline Flavivirus Immune Status, Severity and Treatment Group

Baseline Flavivirus Immune Status	Severity	2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Post Dose 1									
All Subjects	Number of Subjects	x	N/A	x	N/A	x	N/A	x	N/A
	None	xx	Xx	xx	xx	xx	xx	xx	xx
	Mild								
	Moderate								
	Severe								
	Not Reported								
Baseline ZIKV Seropositive	Number of Subjects								
	None								
	Mild								
	Moderate								
	Severe								
	Not Reported								
Baseline ZIKV Seronegative	Number of Subjects								
	None								
	Mild								
	Moderate								
	Severe								
	Not Reported								
Baseline ZIKV Seropositive and DENV Seropositive	Number of Subjects								
	None								
	Mild								
	Moderate								

Table 44: Number and Percentage of Subjects Experiencing Any Local or Systemic Solicited Events through Day 8 Post Vaccination by Dose, Baseline Flavivirus Immune Status, Severity and Treatment Group *(continued)*

	Severe								
	Not Reported								
Baseline DENV Seropositive and DENV Seronegative	Number of Subjects								
	None								
	Mild								
	Moderate								
	Severe								
	Not Reported								
Baseline DENV Seronegative and DENV Seropositive	Number of Subjects								
	None								
	Mild								
	Moderate								
	Severe								
	Not Reported								
Baseline DENV Seronegative and DENV Seronegative	Number of Subjects								
	None								
	Mild								
	Moderate								
	Severe								
	Not Reported								
Repeat for:									
Post Dose 2									
Post Any Dose									
In this table, subjects who reported not having a symptom are listed as “None”, while subjects who did not complete their Memory Aid or could not remember whether they had a symptom are listed as “Not Reported”. Severity is the maximum severity reported post dosing for each subject. N=Number of subjects in the Safety population who received the specified dose.									

Table 44: Number and Percentage of Subjects Experiencing Any Local or Systemic Solicited Events through Day 8 Post Vaccination by Dose, Baseline Flavivirus Immune Status, Severity and Treatment Group *(continued)*

n = Number of subjects reporting an event
For subjects in Group 3 receiving vaccinations in both arms, the maximum severity in either arm is summarized

Table 45: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – All Subjects

Symptom		2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	All Subjects (N=X)
Post Dose 1					
Any Local Reaction	n (%)	x (xx)	x (xx)	x (xx)	x (xx)
	95% CI	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Repeat for:					
Pain					
Erythema					
Induration (mm)					
Induration					
Pruritis					
Ecchymosis					
Tenderness					
Any Systemic Reaction	n (%)	x (xx)	x (xx)	x (xx)	x (xx)
	95% CI	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Repeat for:					
Feverishness					
Fatigue					
Malaise					
Myalgia					
Arthralgia					
Headache					
Nausea					
Vomiting					
Diarrhea					
Abdominal Pain					
Rash					
Fever					
Repeat for:					
Post Dose 2					
Post Any Dose					

Each event is defined as any grade 1, 2 or 3 solicited reaction within 7 days following either dose.
N = Number of subjects in the safety population who received the specified dose; used as the denominator for percentages.
n = Number of subjects reporting an event

Tables with similar format:

Table 46: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – Baseline ZIKV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 47: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – Baseline ZIKV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 48: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 49: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 50: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 51: Number, Percentage and 95% Confidence Interval of Subjects Experiencing Any Grade 1 or Greater Solicited Adverse Event, by Dose, Symptom and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 52: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity and Treatment Group – All Subjects

Local Reactions, Post Dose 1 **All Subjects**							
		2.5 mcg ZPIV (N=X)		**5 mcg ZPIV (N=X)**		**Placebo (N=X)**	
Reaction	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**
Any Local Reaction	None	x	xx	x	xx	x	xx
	Mild						
	Moderate						
	Severe						
	Not Reported						
Repeat for:							
Pain							
Erythema							
Induration (mm)							
Induration							
Pruritis							
Ecchymosis							
Tenderness							
Repeat for:							
Local Reactions, Post Dose 2 **All Subjects**							
Local Reactions, Post Any Dose **All Subjects**							

Subjects who reported not having a symptom are listed as "None", while subjects who did not complete their Memory Aid or could not remember whether they had a symptom are listed as "Not Reported".
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.
N=Number of subjects in the Safety Population who received the specified dose.

n = Number of subjects reporting an event
For subjects receiving vaccinations in both arms, the maximum severity in either arm is summarized

Tables with similar format:

Table 53: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 54: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 55: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 56: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 57: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.]

Table 58: Number and Percentage of Subjects Experiencing Solicited Local Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population with the specified flavivirus immune status at baseline.

Table 59: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – All Subjects

Systemic Symptoms, Post Dose 1							
		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)	
Symptom	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**
Any Systemic Symptom	None	x	xx	x	xx	x	xx
	Mild						
	Moderate						
	Severe						
	Not Reported						
Repeat for:							
Feverishness							
Fatigue							
Malaise							
Myalgia							
Arthralgia							
Headache							
Nausea							
Vomiting							
Diarrhea							
Abdominal Pain							
Rash							
Fever							
Repeat for:							
Systemic Symptoms, Post Dose 2							
Systemic Symptoms, Post Any Dose							

Subjects who reported not having a symptom are listed as "None", while subjects who did not complete their Memory Aid or could not remember whether they had a symptom are listed as "Not Reported".
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.
N=Number of subjects in the Safety Population who received the specified dose.

n = Number of subjects reporting an event
For subjects receiving vaccinations in both arms, the maximum severity in either arm is summarized.

Tables with similar format:

Table 60: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population that were flavivirus seropositive at baseline.]

Table 61: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population that were flavivirus seronegative at baseline.]

Table 62: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population that were flavivirus seropositive at baseline.]

Table 63: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population that were flavivirus seropositive at baseline.]

Table 64: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects

[Implementation note: N = Number of subjects in the Safety population that were flavivirus seropositive at baseline.]

Table 65: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Dose, Reaction, Severity, and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects

[Implementation note: N = Number of subjects in the Safety population that were flavivirus seropositive at baseline.]

Table 66: Number and Percentage of Subjects Experiencing Solicited Local or Systemic Events by Symptom, Severity, and Day Post Dosing – 2.5 mcg ZPIV – Post Dose 1

2.5 mcg ZPIV, All subjects Dose Number = 1 (N=X)																						
Severity	**Pre-Dose**		**30 mins Post-Dose**		**Day 1**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 6**		**Day 7**		**Day 8+**		**Any Post-Dose***	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Reaction																						
None	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mild																						
Moderate																						
Severe																						
Not Reported																						
Repeat for:																						
Solicited Local Events																						
Any Local Reaction																						
Pain																						
Erythema																						
Induration (mm)																						
Induration																						
Pruritis																						
Ecchymosis																						
Tenderness																						
Solicited Systemic Events																						
Any Systemic Reaction																						
Feverishness																						
Fatigue																						
Malaise																						

Table 66: Number and Percentage of Subjects Experiencing Solicited Local or Systemic Events by Symptom, Severity, and Day Post Dosing – 2.5 mcg ZPIV – Post Dose 1

2.5 mcg ZPIV, All subjects Dose Number = 1 (N=X)																						
Severity	**Pre-Dose**		**30 mins Post-Dose**		**Day 1**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 6**		**Day 7**		**Day 8+**		**Any Post-Dose***	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Myalgia																						
Arthralgia																						
Headache																						
Nausea																						
Vomiting																						
Diarrhea																						
Abdominal Pain																						
Rash																						
Fever																						

In this table, subjects who reported not having a symptom are listed as "None".

Subjects who were not seen for assessment nor completed a memory aid, or subjects who could not remember whether they had a symptom are listed as "Not Reported".

N = Number of subjects in the Safety population and dosage group who received the specified dose.

n = Number of subjects reporting an event

Severity is the maximum severity reported post dosing for each subject for each day.

* Maximum severity post dosing for each subject over all days.

Tables with similar format:

2.5 mcg ZPIV

Table 67: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population and dosage group who received the specified dose.]

Table 68: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population and dosage group]

5 mcg ZPIV

Table 69: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety Population and dosage group.]

Table 70: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety Population and dosage group who received the specified dose.]

Table 71: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety Population and dosage group.]

Placebo

Table 72: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety Population and dosage group.]

Table 73: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population and dosage group who received the specified dose.]

Table 74: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety Population and dosage group.]

2.5 mcg ZPIV

Table 75: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – 2.5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 76: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 77: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

5 mcg ZPIV

Table 78: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group and baseline flavivirus immune status who received the specified dose.]

Table 79: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 80: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

Placebo

Table 81: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 82: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 83: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive Subjects – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

2.5 mcg ZPIV

Table 84: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – 2.5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 85: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 86: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status.]

5 mcg ZPIV

Table 87: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 88: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 89: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status.]

Placebo

Table 90: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 91: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 92: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative Subjects – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety Population, dosage group, and baseline flavivirus immune status.]

2.5 mcg ZPIV

Table 93: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – 2.5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 94: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 95: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

5 mcg ZPIV

Table 96: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group and baseline flavivirus immune status who received the specified dose.]

Table 97: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 98: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

Placebo

Table 99: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 100: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 101: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

2.5 mcg ZPIV

Table 102: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – 2.5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 103: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 104: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

5 mcg ZPIV

Table 105: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group and baseline flavivirus immune status who received the specified dose.]

Table 106: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 107: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

Placebo

Table 108: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 109: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 110: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seropositive DENV Seronegative Subjects – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

2.5 mcg ZPIV

Table 111: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – 2.5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 112: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 113: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

5 mcg ZPIV

Table 114: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group and baseline flavivirus immune status who received the specified dose.]

Table 115: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 116: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

Placebo

Table 117: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 118: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 119: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seropositive Subjects – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

2.5 mcg ZPIV

Table 120: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – 2.5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 121: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – 2.5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 122: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – 2.5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

5 mcg ZPIV

Table 123: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – 5 mcg ZPIV – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group and baseline flavivirus immune status who received the specified dose.]

Table 124: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – 5 mcg ZPIV – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 125: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – 5 mcg ZPIV – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

Placebo

Table 126: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – Placebo – Post Dose 1

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 127: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – Placebo – Post Dose 2

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status who received the specified dose.]

Table 128: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Severity, and Day Post Dosing – Baseline ZIKV Seronegative DENV Seronegative Subjects – Placebo – Post Any Dose

[Implementation note: N = Number of subjects in the Safety population, dosage group, and baseline flavivirus immune status.]

14.3.1.2 Unsolicited Adverse Events

Table 129: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Severity, Relationship to Study Treatment, and Baseline Flavivirus Immune Status – 2.5 mcg ZPIV

All subjects (N*=X)																			
MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence			Severity									Relationship to Treatment					
					Mild			Moderate			Severe			Not Related			Related		
		n	%	m	n	%	m	n	%	m	n	%	m	n	%	m	n	%	m
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT																		
	[PT 1]																		
	[PT 2]																		
[SOC 2]	Any PT																		
	[PT 1]																		
	[PT 2]																		
Repeat For:																			
Baseline ZIKV Seropositive																			
Baseline ZIKV Seronegative																			
Baseline ZIKV Seropositive and DENV Seropositive																			
Baseline ZIKV Seropositive and DENV Seronegative																			
Baseline ZIKV Seronegative and DENV Seropositive																			
Baseline ZIKV Seronegative and DENV Seronegative																			
N* = Number of subjects in the Safety population with the specified baseline flavivirus immune status. used as denominator for percentages; n=Number of subjects reporting the event; m= Number of events. Table includes all events reported per subject from first administration of study vaccine through 28 days after the last vaccination.																			

Tables with similar format:

Table 130: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Severity, Relationship to Study Treatment, and Baseline Flavivirus Immune Status – 5 mcg ZPIV

Table 131: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Severity, Relationship to Study Treatment, and Baseline Flavivirus Immune Status – Placebo

Table 132: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Severity, Dose, and Baseline Flavivirus Immune Status – 2.5 mcg ZPIV

Baseline Flavivirus Immune Status	MedDRA System Organ Class	Preferred Term	Severity	Post-Dose 1 (N = X)				Post-Dose 2 (N = X)				Post-Any Dose (N = X)			
				n	%	95% CI	m	n	%	95% CI	m	n	%	95% CI	m
All Subjects (N*=X)	Any SOC	Any PT	Any Severity	xx	xx	xx.x, xx.x	xx	xx	xx	xx.x, xx.x	xx	xx	xx	xx.x, xx.x	xx
			Mild												
			Moderate												
			Severe												
	[SOC 1]	Any PT	Any Severity												
			Mild												
			Moderate												
			Severe												
		[PT 1]	Any Severity												
			Mild												
			Moderate												
			Severe												
Repeat for:															
Baseline ZIKV Seropositive (N* = X)															
Baseline ZIKV Seronegative (N* = X)															
Baseline ZIKV Seropositive and DENV Seropositive															

Table 132: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Severity, Dose, and Baseline Flavivirus Immune Status – 2.5 mcg ZPIV *(continued)*

Baseline Flavivirus Immune Status	MedDRA System Organ Class	Preferred Term	Severity	Post-Dose 1 (N = X)				Post-Dose 2 (N = X)				Post-Any Dose (N = X)			
				n	%	95% CI	m	n	%	95% CI	m	n	%	95% CI	m
(N* = X)															
Baseline ZIKV Seropositive and DENV Seronegative (N* = X)															
Baseline ZIKV Seronegative and DENV Seropositive (N* = X)															
Baseline ZIKV Seronegative and DENV Seronegative (N* = X)															

N = Number of subjects in the Safety Population who received the specified dose; N* = Number of subjects in the Safety population with the specified baseline flavivirus immune status. used as denominator for percentages; n=Number of subjects reporting an event under the SOC and PT combination; m = Number of events under the SOC and PT combination.

Post dose columns include events reported within 28 days following the dose; Post-Any Dose column includes events reported within 28 days following either dose.

95% CI = 95% exact Clopper-Pearson confidence interval

Tables with similar format:

Table 133: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Severity, Dose, and Baseline Flavivirus Immune Status – 5 mcg ZPIV

Table 134: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class, Preferred Term, Severity, Dose, and Baseline Flavivirus Immune Status – Placebo

Table 135: Number and Percentage of Subjects Reporting NOCMCs by MedDRA System Organ Class, Preferred Term, Treatment Group, and Baseline Flavivirus Immune Status

			2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
Baseline Flavivirus Immune Status	**MedDRA System Organ Class**	**MedDRA Preferred Term**	**n**	**%**	**95 % CI**	**m**	**n**	**%**	**95 % CI**	**m**	**n**	**%**	**95 % CI**	**m**	**n**	**%**	**95 % CI**	**m**
All Subjects (N* = X)	Any SOC	Any PT	x	xx	xx.x, xx.x	x	x	xx	xx.x, xx.x	x	x	xx	xx.x, xx.x	x	x	xx	xx.x, xx.x	x
	[SOC 1]	Any PT																
		[PT 1]																
		[PT 2]																
	[SOC 2]	Any PT																
		[PT 1]																
		[PT 2]																
Repeat for:																		
Baseline ZIKV Seropositive (N* = X)																		
Baseline ZIKV Seronegative (N* = X)																		
Baseline ZIKV Seropositive and DENV Seropositive (N* = X)																		
Baseline ZIKV Seropositive and DENV Seronegative (N* = X)																		
Baseline ZIKV Seronegative and DENV Seropositive (N* = X)																		
Baseline ZIKV Seronegative and DENV Seronegative (N* = X)																		

N = Number of subjects in the Safety population; N* = Number of subjects in the Safety population with the specified baseline flavivirus immune status used as the denominator for percentages; n =Number of subjects reporting an event under the SOC and PT combination; m = Number of events under the SOC and PT combination.
Table includes events reported from time of first administration of study vaccine through 28 days after the last vaccination.

Table with similar format:

Table 136: Number and Percentage of Subjects Reporting AESIs Related to Study Treatment by MedDRA System Organ Class, Preferred Term, Treatment Group, and Baseline Flavivirus Immune Status

Table 137: Duration (Days) of AESIs Related to Study Treatment by MedDRA System Organ Class, Preferred Term, Treatment Group, and Baseline Flavivirus Immune Status

Baseline Flavivirus Immune Status	MedDRA System Organ Class	MedDRA Preferred Term	Statistic	2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	All Subjects (N=X)
All Subjects (N*=X)	Any SOC	Any PT	n	x	x	x	x
			Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
			Median	x.x	x.x	x.x	x.x
			Min, Max	x, x	x, x	x, x	x, x
		[PT 1]	n				
			Mean (SD)				
			Median				
			Min, Max				
	[SOC 1]	Any PT	n				
			Mean (SD)				
			Median				
			Min, Max				
		[PT 1]	n				
			Mean (SD)				
			Median				
			Min, Max				
	[SOC 2]	Any PT	n				
			Mean (SD)				
			Median				
			Min, Max				
		[PT 1]	n				
			Mean (SD)				
			Median				
			Min, Max				

Table 137: Duration (Days) of AESIs Related to Study Treatment by MedDRA System Organ Class, Preferred Term, Treatment Group, and Baseline Flavivirus Immune Status *(continued)*

Baseline Flavivirus Immune Status	MedDRA System Organ Class	MedDRA Preferred Term	Statistic	2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	All Subjects (N=X)
Repeat for:							
Baseline ZIKV Seropositive (N* = X)							
Baseline ZIKV Seronegative (N* = X)							
Baseline ZIKV Seropositive and DENV Seropositive (N* = X)							
Baseline ZIKV Seropositive and DENV Seronegative (N* = X)							
Baseline ZIKV Seronegative and DENV Seropositive (N* = X)							
Baseline ZIKV Seronegative and DENV Seronegative (N* = X)							
N = Number of subjects in the Safety population; N* = Number of subjects in the Safety population with the specified flavivirus status used as the denominator for percentages; n = number of subjects reporting an AESI related to study treatment							

Table with similar format to Table 110:

Table 138: Number and Percentage of Subjects Reporting Serious Adverse Events Related to Study Treatment by MedDRA System Organ Class, Preferred Term, Treatment Group, and Baseline Flavivirus Immune Status

Table with similar format to Table 111:

Table 139: Duration (Days) of Serious Adverse Events Related to Study Treatment by MedDRA System Organ Class, Preferred Term, Treatment Group, and Baseline Flavivirus Immune Status

Table 140: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – All Subjects

[Implementation note: This table can include any subjects who did not have a baseline flavivirus status observed.]

	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
Infection Confirmation Status	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**
All Events	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x
Events Requiring Concomitant Medication																
Events Requiring Medical Treatment[a]																

N = Number of subjects in the Safety population
%=percentage of subjects reporting at least one AFI/ARI event out of total number of subjects in the Safety population in the group
95% CI is calculated using the Clopper-Pearson methodology for a binomial distribution.
This table includes subjects who only received dose 1.

[c]Includes hospitalization or other medical care

Tables with similar format:

Table 141: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive Subjects

[Implementation note: If no subjects are flavivirus positive at baseline, replace this table with the following note: 'Table not generated since no positive arbovirus results were reported for ZIKV or DENV.']

Table 142: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative Subjects

Table 143: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 144: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 145: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 146: Summary of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects

Table 147: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – All Subjects

[Implementation note: This table can include any subjects who did not have a baseline flavivirus status observed.]

	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
Infection Confirmation Status	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**	**Number of Events**	**Number of Subjects**	**% of Subjects**	**95% CI**
Positive by PCR[a]	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x
Positive by 4-Fold Titer Rise[b]																
Any Positive Confirmation[a,b]																
Negative Lab Confirmation																

N = Number of subjects in the Safety Population
%=percentage of subjects reporting at least one AFI/ARI event/total number of subjects in the Safety population in the group
95% CI is calculated using the Clopper-Pearson methodology for a binomial distribution.
This table includes subjects who only received dose 1.
[a] PCR confirmation includes a positive PCR result for at least one of ZIKV (blood or urine) or DENV.
[b] 4-fold rise in either ZIKV or DENV neutralization titers after the ARI/AFI illness visit compared to before the illness visit.
[c]Includes hospitalization or other medical care

Tables with similar format:

Table 148: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – Baseline ZIKV Seropositive Subjects

Table 149: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – Baseline ZIKV Seronegative Subjects

Table 150: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 151: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 152: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 153: Number of Laboratory Confirmed ZIKV or DENV Infections Overall and by Confirmation Method – Baseline ZIKV Seronegative and DENV Seronegative Subjects

Table 154: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – All Subjects

[Implementation note: This table can include any subjects who did not have a baseline flavivirus status observed.]

	2.5 mcg ZPIV (N*=X)				5 mcg ZPIV (N*=X)				Placebo (N*=X)				All Subjects (N*=X)			
Infection Confirmation Status	**Number of Subjects**	**Number of Events**	**% of Events**	**95% CI**	**Number of Subjects**	**Number of Events**	**% of Events**	**95% CI**	**Number of Subjects**	**Number of Events**	**% of Events**	**95% CI**	**Number of Subjects**	**Number of Events**	**% of Events**	**95% CI**
All Events																
Positive by PCR[a]	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x	x	x	xx	x.x, x.x
Positive by 4-Fold Titer Rise[b]																
Any Positive Confirmation[a,b]																
Negative Lab Confirmation																
Events Requiring Concomitant Medication																
Positive by PCR[a]																
Positive by 4-Fold Titer Rise[b]																
Any Positive Confirmation[a,b]																
Negative Lab Confirmation																
Events Requiring Medical Treatment[c]																
Positive by PCR[a]																
Positive by 4-Fold Titer Rise[b]																
Any Positive Confirmation[a,b]																
Negative Lab Confirmation																

N* = Total number of AFI/ARI events
%= number of AFI/ARI events / total number of AFI/ARI events (N*)
95% CI is calculated using the Clopper-Pearson methodology for a binomial distribution.
This table includes subjects who only received dose 1.
[a] PCR confirmation includes a positive PCR result for at least one of ZIKV (blood or urine) or DENV.
[b] 4-fold rise in either ZIKV or DENV neutralization titers after the ARI/AFI illness visit compared to before the illness visit.
[c]Includes hospitalization or other medical care

Tables with similar format:

Table 155: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – Baseline ZIKV Seropositive Subjects

Table 156: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – Baseline ZIKV Seronegative Subjects

Table 157: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 158: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 159: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 160: Summary of ARI/AFI Events Occurring Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Status and Confirmation Method – Baseline ZIKV Seronegative and DENV Seronegative Subjects

Table 161: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – All Subjects

[Implementation Note: If 100% of subject in all groups are counted in the "None" rows, then suppress the "Mild", "Moderate", and "Severe" columns. This table can include any subjects who did not have a baseline flavivirus status observed.]

	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Symptom	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Symptom	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Fever																
Feverishness																
Lethargy																
Restlessness																
Rash not at injection site																
Nonpurulent conjunctivitis																
Headache																
Respiratory distress																
Retro-orbital pain																
Myalgia/Muscle pain																
Arthralgia/Joint pain																
Arthritis																
Nausea																
Abdominal pain																
Vomiting*																
Persistent vomiting*																
Bleeding*																

Table 161: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – All Subjects

	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Symptom	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

N = number of subjects reporting at least one AFI/ARI
n=number of subjects reporting the symptom
%=percentage of subjects reporting the symptom out of the total number of subjects reporting at least one AFI/ARI
If multiple AFI/ARI are reported for a subject, then the maximum severity is considered for each symptom.
This table includes subjects who only received dose 1.

* Reported as None/Any

Tables with similar format:

Table 162: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive Subjects

Table 163: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative Subjects

Table 164: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 165: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 166: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 167: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects

Table 168: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – All Subjects

[Implementation Note: If 100% of AFI/ARI events in all columns are counted in the "None" rows, then suppress the "Mild", "Moderate", and "Severe" columns. This table can include any subjects who did not have a baseline flavivirus status observed.]

Infection Confirmation Status	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Symptom																
Positive by PCR[a] (N*=X)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Positive by 4-Fold Titer Rise[b] (N*=X)																
Any Positive Confirmation[a,b] (N*=X)																
Negative Lab Confirmation (N*=X)																
Repeat for:																
Fever																
Feverishness																
Lethargy																
Restlessness																
Rash not at injection site																
Nonpurulent conjunctivitis																
Headache																
Respiratory distress																
Retro-orbital pain																
Myalgia/Muscle pain																
Arthralgia/Joint pain																
Arthritis																
Nausea																
Abdominal pain																
Vomiting*																
Persistent vomiting*																

Table 168: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – All Subjects *(continued)*

Infection Confirmation Status	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bleeding*																

N = number of subjects reporting at least one AFI/ARI
N* = Number of subjects with ARI/AFI and specified confirmation results n = number of subjects reporting the symptom
%=number of subjects reporting the symptom out of N*
If multiple AFI/ARI are reported for a subject, then the maximum severity is considered for each symptom. "4-Fold Rise" refers to at least a 4-fold rise in ZIKV or DENV MN50 titers after the AFI/ARI illness visit compared to before the illness visit.
This table includes subjects who only received dose 1.
* Reported as None/Any

Tables with similar format:

Table 169: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – Baseline ZIKV Seropositive Subjects

Table 170: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – Baseline ZIKV Seronegative Subjects

Table 171: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 172: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 173: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 174: Maximum Severity of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by ZIKV or DENV Infection Confirmation Status and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects

Table 175: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – All Subjects

[Implementation note: This table can include any subjects who did not have a baseline flavivirus status observed.]

Symptom	2.5 mcg ZPIV (N=X)				5 mcg ZPIV (N=X)				Placebo (N=X)				All Subjects (N=X)			
	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
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	x, x	x	x.x (x.x)	x.x	x, x
Repeat for:																
Fever																
Feverishness																
Lethargy																
Restlessness																
Rash not at injection site																
Nonpurulent conjunctivitis																
Headache																
Respiratory distress																
Retro-orbital pain																
Myalgia/Muscle pain																
Arthralgia/Joint pain																
Arthritis																
Nausea																
Abdominal pain																
Vomiting*																
Persistent vomiting*																
Bleeding*																

Table 175: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – All Subjects *(continued)*

Symptom	2.5 mcg ZPIV (N=X)	5 mcg ZPIV (N=X)	Placebo (N=X)	All Subjects (N=X)
N = number of subjects reporting at least one AFI/ARI n = number of subjects reporting the symptom If multiple AFI/ARI are reported for a subject, then the maximum severity is considered for each symptom; if multiple AFI/ARI are reported for a subject, then the maximum duration is considered for each symptom This table includes subjects who only received dose 1. * Reported as None/Any				

Tables with similar format:

Table 176: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive Subjects

Table 177: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative Subjects

Table 178: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 179: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 180: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 181: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects

Table 182: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – All Subjects

[Implementation note: This table can include any subjects who did not have a baseline flavivirus status observed.]

Symptom	Infection Confirmation Status	2.5 mcg ZPIV (N*=X)				5 mcg ZPIV (N*=X)				Placebo (N*=X)				All Subjects (N*=X)			
		n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
Any Symptom	Positive by PCR[a]	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
	Positive by 4-Fold Titer Rise[b]																
	Any Positive Confirmation[a,b]																
	Negative Lab Confirmation																
Fever																	
Feverishness																	
Lethargy																	
Restlessness																	
Rash not at injection site																	
Nonpurulent conjunctivitis																	
Headache																	
Respiratory distress																	
Retro-orbital pain																	
Myalgia/Muscle pain																	
Arthralgia/Joint pain																	
Arthritis																	

Table 182: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – All Subjects *(continued)*

Symptom	Infection Confirmation Status	2.5 mcg ZPIV (N*=X)				5 mcg ZPIV (N*=X)				Placebo (N*=X)				All Subjects (N*=X)			
		n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
Nausea																	
Abdominal pain																	
Vomiting*																	
Persistent vomiting*																	
Bleeding*																	

N* = number of subjects reporting at least one AFI/ARI
n = number of subjects reporting the symptom
If multiple AFI/ARI are reported for a subject, then the maximum severity is considered for each symptom; if multiple AFI/ARI are reported for a subject, then the maximum duration is considered for each symptom.
This table includes subjects who only received dose 1.
[a] PCR confirmation includes a positive PCR result for at least one of ZIKV (blood or urine) or DENV.
[b] 4-fold rise in either ZIKV or DENV neutralization titers after the ARI/AFI illness visit compared to before the illness visit.
* Reported as None/Any

Table with similar format:

Table 183: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – Baseline ZIKV Seropositive Subjects

Table 184: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – Baseline ZIKV Seronegative Subjects

Table 185: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – Baseline ZIKV Seropositive and DENV Seropositive Subjects

Table 186: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – Baseline ZIKV Seropositive and DENV Seronegative Subjects

Table 187: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – Baseline ZIKV Seronegative and DENV Seropositive Subjects

Table 188: Duration (Days) of Symptoms of AFI/ARI Events Reported Through 12 Months Post Final Vaccination by Treatment Group and ZIKV or DENV Infection Confirmation Status – Baseline ZIKV Seronegative and DENV Seronegative Subjects

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 189: Listing of Serious Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , Baseline Flavivirus Immune Status:, AE Number:												
Comments:												
Subject ID: , Treatment Group: , Baseline Flavivirus Immune Status:, AE Number:												
Comments:												
Listing includes serious adverse events reported at any time during the study.												

Table 190: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , Baseline Flavivirus Immune Status:, AE Number:										
Comments:										
Subject ID: , Treatment Group: , Baseline Flavivirus Immune Status:, AE Number:										
Comments:										

Table 191: Listing of AESIs and NOCMCs

[Implementation Note: sort order is Subject ID, Number of Doses Received at Time of Event, and Date of Product Administration.]

Adverse Event	Number of Doses Received at Time of Event	No. of Days Post Associated Dose	Duration of Event	Severity	MedDRA System Organ Class	AESI?	NOCMC?	Relationship	Outcome
Subject ID: , Treatment Group: , Baseline Flavivirus Immune Status:, AE Number:									
Comments:									
Subject ID: , Treatment Group: , Baseline Flavivirus Immune Status:, AE Number:									
Comments:									

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

[Placeholder for the CSR]

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 192: Listing of Abnormal Laboratory Results – Chemistry

Subject ID	Treatment Group	Baseline Flavivirus Immune Status	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

Tables with similar format:

Table 193: Listing of Abnormal Laboratory Results – Hematology

Table 194: Listing of Abnormal Laboratory Results – Urinalysis

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 195: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Any Chemistry Parameter

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
All Subjects												
Baseline	2.5 mcg ZPIV	x	x	xx	x	xx	x	xx	x	xx	x	xx
	5 mcg ZPIV											
	Placebo											
	All Subjects											
Repeat for:												
Day 8												
Day 15												
Day 36												
Day 43												
Max Severity Post Baseline												
Repeat for:												
Baseline ZIKV Seropositive												
Baseline ZIKV Seronegative												
Baseline ZIKV Seropositive and DENV Seropositive												
Baseline ZIKV Seropositive and DENV Seronegative												
Baseline ZIKV Seronegative and DENV Seropositive												
Baseline ZIKV Seronegative and DENV Seronegative												

N=Number of subjects in the Safety population who completed the specified visit.
The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 196: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – ALT

Table 197: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – AST

Table 198: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Total Bilirubin

Table 199: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – BUN

Table 200: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Creatinine

Table 201: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Any Chemistry Parameter

Time Point	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
			n	%	n	%	n	%
All Subjects								
Day 8	2.5 mcg ZPIV	x	x	xx	x	xx	x	xx
	5 mcg ZPIV							
	Placebo							
	All Subjects							
Repeat for:								
Day 15								
Day 36								
Day 43								
Max Severity Post Baseline								
Repeat for:								
Baseline ZIKV Seropositive								
Baseline ZIKV Seronegative								
Baseline ZIKV Seropositive and DENV Seropositive								
Baseline ZIKV Seropositive and DENV Seronegative								
Baseline ZIKV Seronegative and DENV Seropositive								
Baseline ZIKV Seronegative and DENV Seronegative								

N=Number of subjects in the safety population who completed the specified visit and results are available.

The "Max Severity Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 202: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – ALT

Table 203: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – AST

Table 204: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Total Bilirubin

Table 205: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – BUN

Table 206: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Creatinine

Table 207: Laboratory Summary Statistics by Time Point and Treatment Group – ALT

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
All Subjects						
Baseline	2.5 mcg ZPIV	xx	xx.x	xx.x	xx	xx, xx
	5 mcg ZPIV					
	Placebo					
	All Subjects					
Repeat for:						
Day 8						
Day 8, Change from Baseline						
Day 15						
Day 15, Change from Baseline						
Day 36						
Day 36, Change from Baseline						
Day 43						
Day 43, Change from Baseline						
Repeat for:						
Baseline ZIKV Seropositive						
Baseline ZIKV Seronegative						
Baseline ZIKV Seropositive and DENV Seropositive						
Baseline ZIKV Seropositive and DENV Seronegative						
Baseline ZIKV Seronegative and DENV Seropositive						
Baseline ZIKV Seronegative and DENV Seronegative						
N=Number of subjects in the Safety population who completed the specified visit and results are available.						

Tables with similar format:

Table 208: Laboratory Summary Statistics by Time Point and Treatment Group – AST

Table 209: Laboratory Summary Statistics by Time Point and Treatment Group – Total Bilirubin

Table 210: Laboratory Summary Statistics by Time Point and Treatment Group – BUN

Table 211: Laboratory Summary Statistics by Time Point and Treatment Group – Creatinine

14.3.5.2 Hematology Results

Table with format similar to Table 195:

Table 212: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Any Hematology Parameter

Table 213: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – WBC

Time Point	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
All Subjects																		
Baseline	2.5 mcg ZPIV	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	5 mcg ZPIV																	
	Placebo																	
	All Subjects																	
Repeat for:																		
Day 8																		
Day 15																		
Day 36																		
Day 43																		
Max Severity Post Baseline																		
Repeat for:																		
Baseline ZIKV Seropositive																		
Baseline ZIKV Seronegative																		
Baseline ZIKV Seropositive and DENV Seropositive																		
Baseline ZIKV Seropositive and DENV Seronegative																		
Baseline ZIKV Seronegative and DENV Seropositive																		
Baseline ZIKV Seronegative and DENV Seronegative																		

N=Number of subjects in the Safety population who completed the specified visit.

The "Max Severity Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table with format similar to Table 195:

Table 214: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status–Hemoglobin

Table with format similar to Table 213:

Table 215: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status–Hematocrit

Table with format similar to Table 195:

Table 216: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status–Platelet Count

Table with format similar to Table 201:

Table 217: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Any Hematology Parameter

Table 218: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status– WBC

Time Point	Treatment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)	
			n	%	n	%	n	%	n	%	n	%	n	%
All Subjects														
Day 8	2.5 mcg ZPIV	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	5 mcg ZPIV													
	Placebo													
	All Subjects													
Repeat for:														
Day 15														
Day 36														
Day 43														
Max Severity Post Baseline														
Repeat for:														
Baseline ZIKV Seropositive														
Baseline ZIKV Seronegative														
Baseline ZIKV Seropositive and DENV Seropositive														
Baseline ZIKV Seropositive and DENV Seronegative														
Baseline ZIKV Seronegative and DENV Seropositive														
Baseline ZIKV Seronegative and DENV Seronegative														

N=Number of subjects in the safety population who completed the specified visit and results are available.

The "Max Severity Post Baseline" rows indicate the maximum severity of abnormal laboratory results related to study treatment experienced by each subject at any time point post baseline, including unscheduled assessments.

Table with format similar to Table 201:

Table 219: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Hemoglobin

Table with format similar to Table 218:

Table 220: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Hematocrit

Table with format similar to Table 201:

Table 221: Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Platelet Count

Tables with format similar to Table 207:

Table 222: Laboratory Summary Statistics by Time Point and Treatment Group – WBC

Table 223: Laboratory Summary Statistics by Time Point and Treatment Group – Hemoglobin

Table 224: Laboratory Summary Statistics by Time Point and Treatment Group – Hematocrit

Table 225: Laboratory Summary Statistics by Time Point and Treatment Group – Platelet Count

14.3.5.3 Urinalysis Results

Tables with format similar to Table 195:

Table 226: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Any Urinalysis Parameter

Table 227: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Urine Protein

Table 228: Laboratory Results by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status– Urine Glucose

Tables with format similar to Table 201:

Table 229: **Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Any Urinalysis Parameter**

Table 230: **Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Urine Protein**

Table 231: **Abnormal Laboratory Results Related to Study Treatment by Maximum Severity, Time Point, Treatment Group, and Baseline Flavivirus Immune Status – Urine Glucose**

14.3.6 Displays of Vital Signs

Table 232: Vital Signs by Maximum Severity, Time Point and Treatment Group – Any Assessment

Time Point	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Any Severity	
			n	%	n	%	n	%	n	%	n	%
Baseline	2.5 mcg ZPIV	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
	5 mcg ZPIV											
	Placebo											
	All Subjects											
Repeat for:												
Day 1												
Day 2												
Day 8												
Day 15												
Day 29												
Day 30												
Day 36												
Day 43												
Day 57												
Max Severity Post Baseline												

N=Number of subjects in the Safety population who completed the specified visit and have any vital signs data available from the visit.
The "Max Severity Post Baseline" rows indicates the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 233: Vital Signs by Maximum Severity, Time Point and Treatment Group – Oral Temperature

Table 234: Vital Signs by Maximum Severity, Time Point and Treatment Group – Pulse

Table 235: Vital Signs by Maximum Severity, Time Point and Treatment Group – Systolic Blood Pressure

Table 236: Vital Signs by Maximum Severity, Time Point and Treatment Group – Diastolic Blood Pressure

14.4 Summary of Concomitant Medications

Table 237: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

		2.5 mcg ZPIV (N=X)		5 mcg ZPIV (N=X)		Placebo (N=X)		All Subjects (N=X)	
WHO Drug Code Level 1, Anatomic Group	**WHO Drug Code Level 2, Therapeutic Subgroup**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Level 1 Code	Any Level 2 Code	x	xx	x	xx	x	xx	x	xx
[Level 1, Code 1]	[Any Level 1, Code 1]								
	[Level 2, Code 1]								
	[Level 2, Code 2]								
	[Etc.]								
[Level 1, Code 2]	[Any Level 1, Code 2]								
	[Level 2, Code 1]								
	[Level 2, Code 2]								
	[Etc.]								
[Etc.]	Any								
	[Level 2, Code 1]								
	[Level 2, Code 2]								
	[Etc.]								

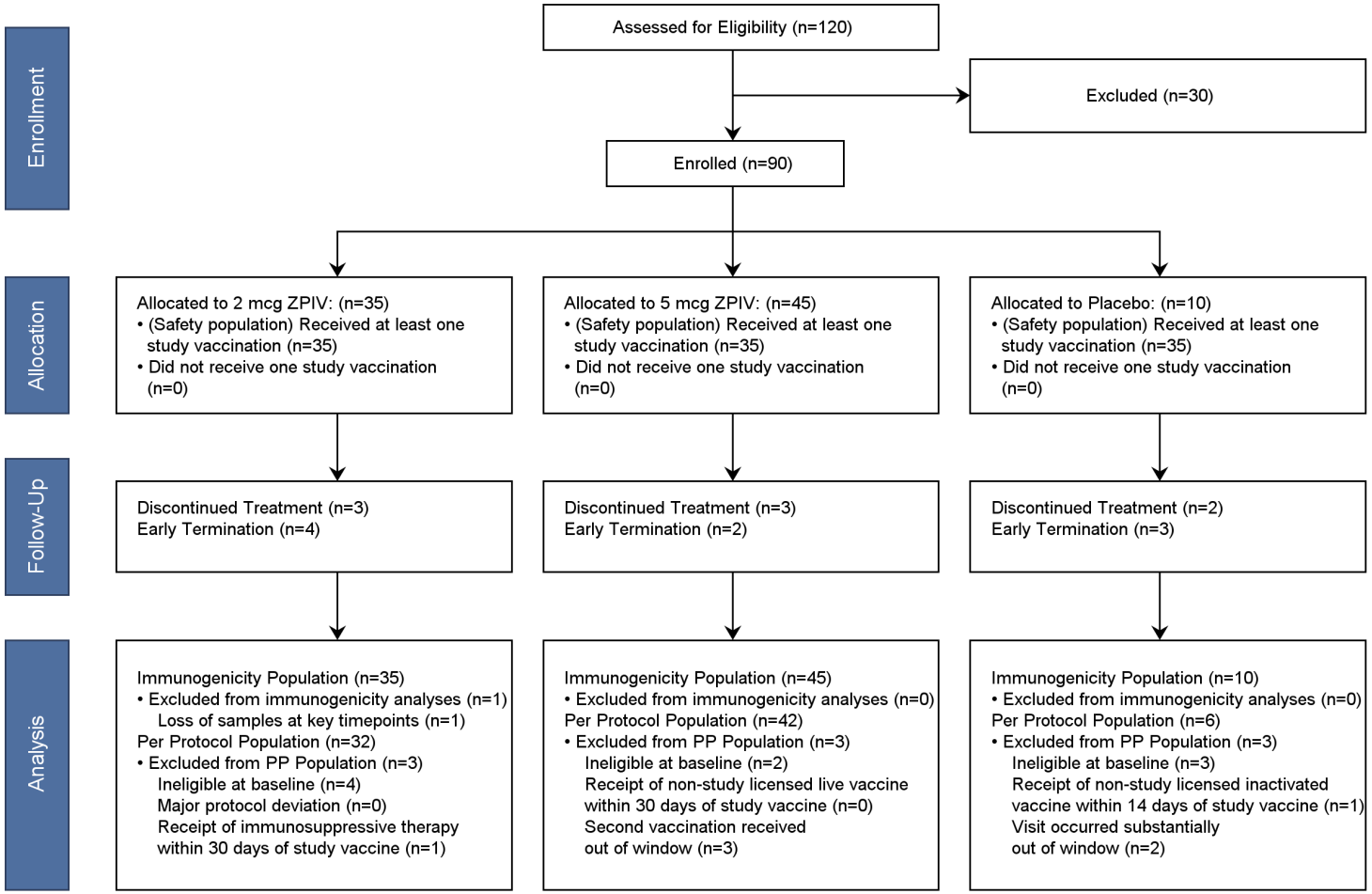
N = Number of subjects in the Safety population
n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

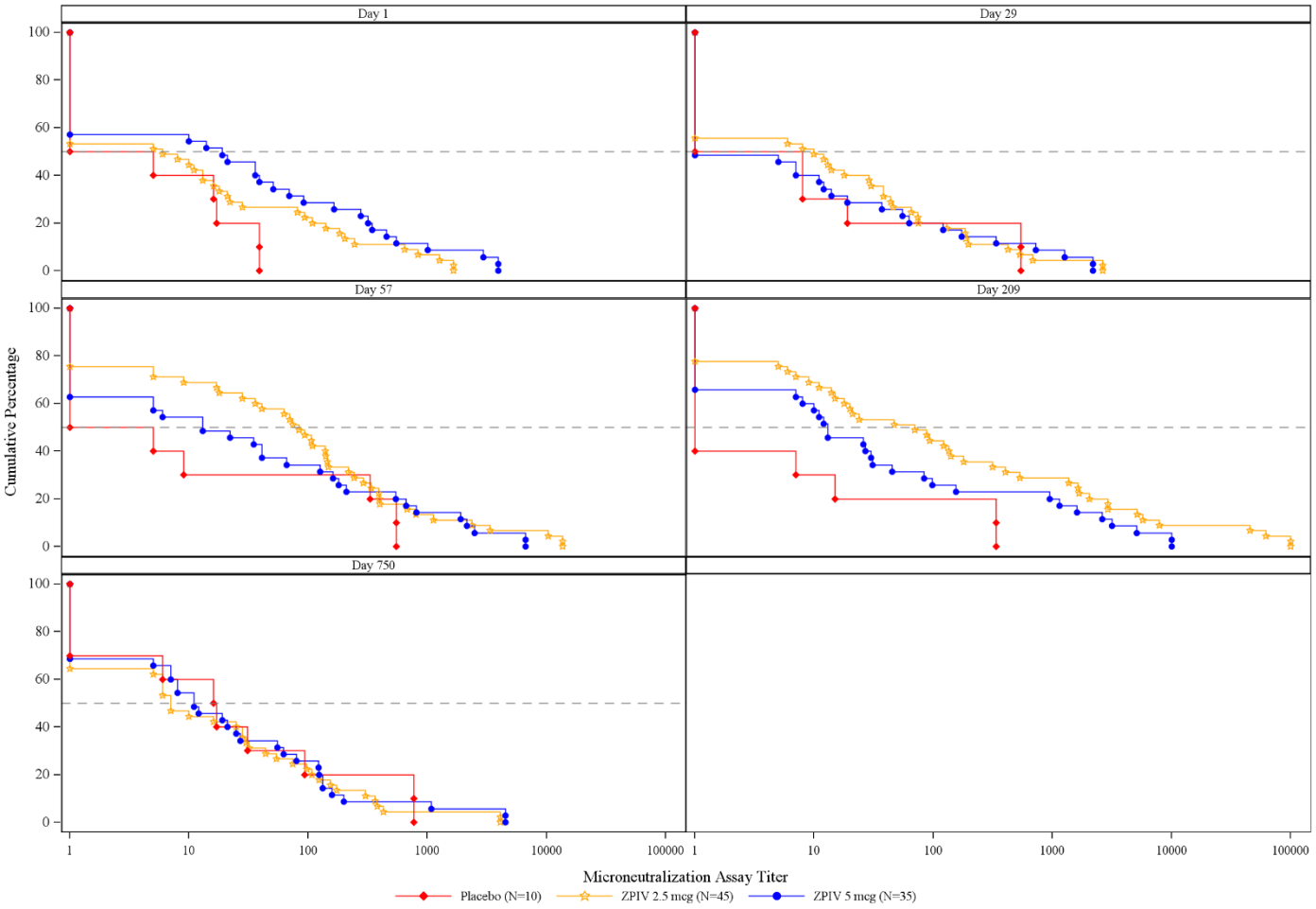
10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram



14.2.2 Immunogenicity Response Figures by Measure, Treatment Group, and Time Point

Figure 2: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – All Subjects – Immunogenicity Population



Figures with format similar to Figure 2:

Figure 3: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – All Subjects – Per Protocol Population

Figure 4: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seropositive Subjects – Immunogenicity Population

Figure 5: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seropositive Subjects – Per Protocol Population

Figure 6: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seronegative Subjects – Immunogenicity Population

Figure 7: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seronegative Subjects, – Per Protocol Population

Figure 8: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Immunogenicity Population

Figure 9: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Per Protocol Population

Figure 10: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects – Immunogenicity Population

Figure 11: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects – Per Protocol Population

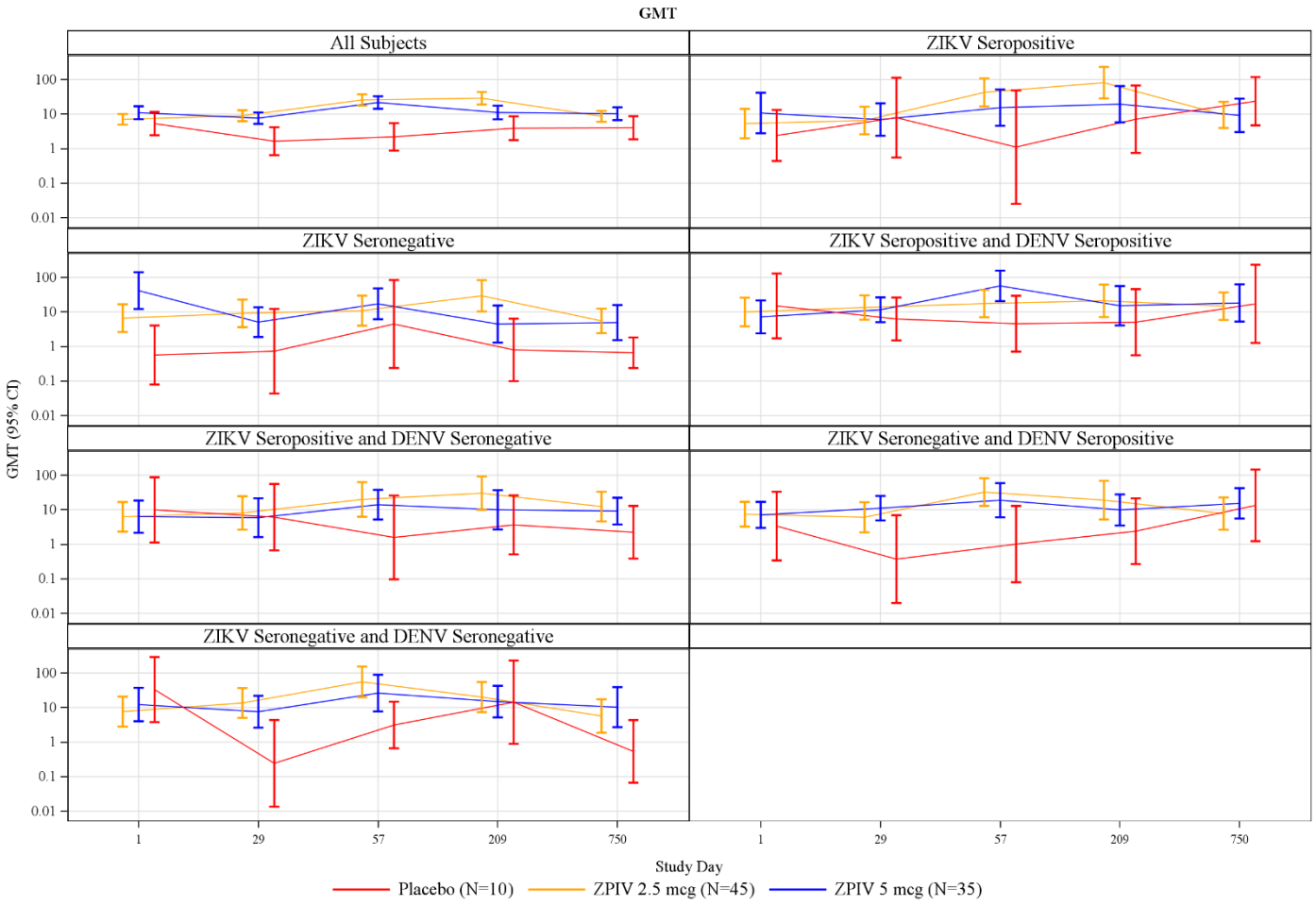
Figure 12: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects – Immunogenicity Population

Figure 13: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects – Per Protocol Population

Figure 14: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects – Immunogenicity Population

Figure 15: Reverse Cumulative Distribution of ZIKV Microneutralization Assay (MN50) Titer by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects – Per Protocol Population

Figure 16: Geometric Mean ZIKV Microneutralization (MN50) Titer (GMT), by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

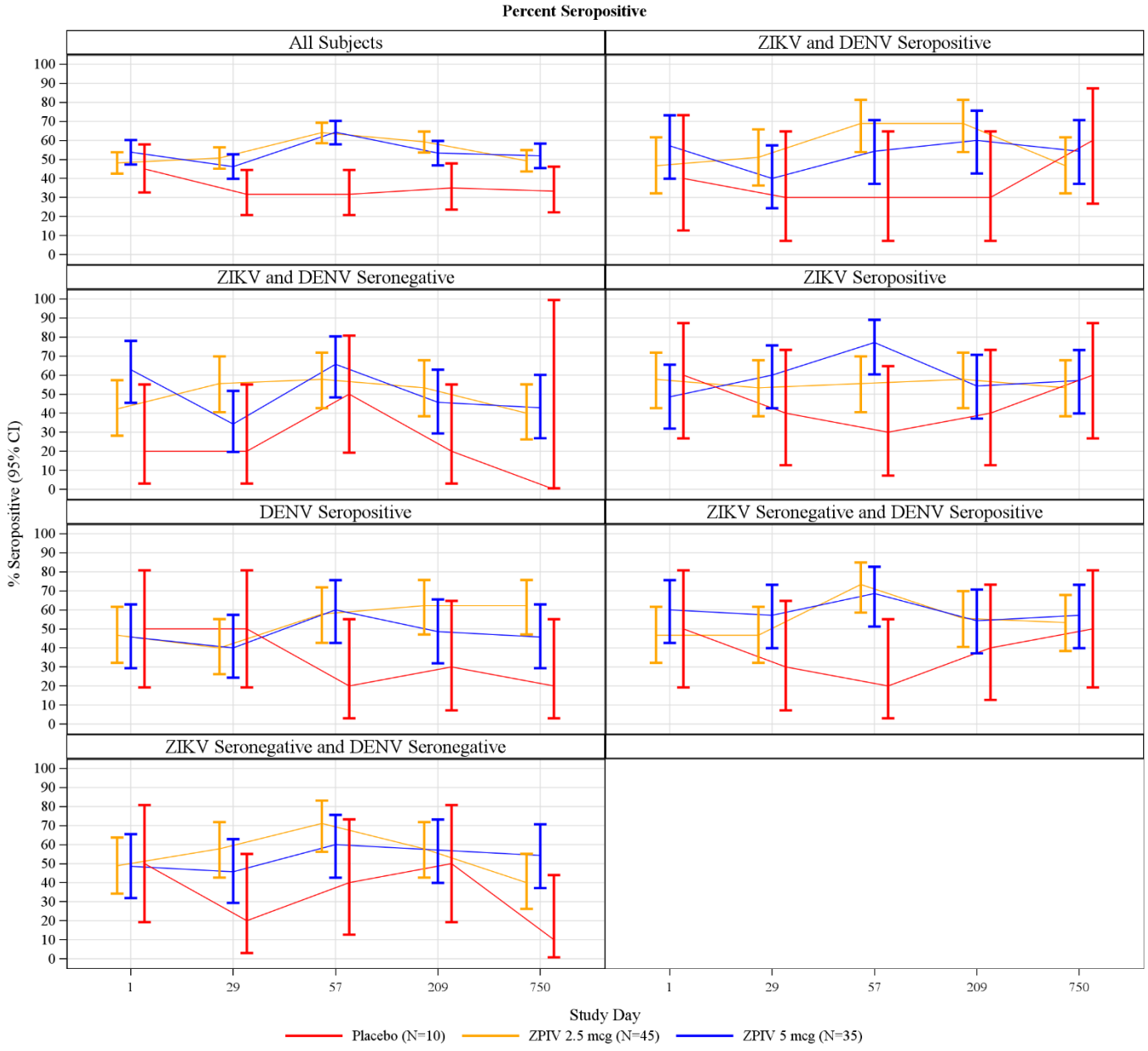


Note: The bars represent the upper and lower limits of the 95% confidence interval for GMT.

Figure with similar format:

Figure 17: Geometric Mean ZIKV Microneutralization (MN50) Titer (GMT), by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

Figure 18: Percent of Subjects Seropositive at Threshold of ≥10 of ZIKV Microneutralization (MN50) Assay, by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population



Note: The bars represent the upper and lower limits of the 95% confidence interval for the percent of subjects seropositive.

Figures with similar format:

Figure 19: Percent of Subjects Seropositive at Threshold of ≥10 of ZIKV Microneutralization (MN50) Assay, by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

Figure 20: Percent of Subjects Seropositive at Threshold of ≥100 of ZIKV Microneutralization (MN50) Assay, by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

Figure 21: Percent of Subjects Seropositive at Threshold of ≥100 of ZIKV Microneutralization (MN50) Assay, by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

Figure 22: Percent Seroconversion (≥4-Fold Rise from Baseline) of ZIKV Microneutralization (MN50) Assay, by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

Figure 23: Percent Seroconversion (≥4-Fold Rise from Baseline) of ZIKV Microneutralization (MN50) Assay, by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

Same formats as Figure 2 to Figure 23:

RCD Curves

Figure 24: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – All Subjects – Immunogenicity Population

Figure 25: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – All Subjects – Per Protocol Population

Figure 26: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seropositive Subjects – Immunogenicity Population

Figure 27: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seropositive Subjects – Per Protocol Population

Figure 28 Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seronegative Subjects – Immunogenicity Population

Figure 29: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seronegative Subjects – Per Protocol Population

Figure 30: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Immunogenicity Population

Figure 31: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seropositive Subjects – Per Protocol Population

Figure 32: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects – Immunogenicity Population

Figure 33: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seropositive and DENV Seronegative Subjects – Per Protocol Population

Figure 34 Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects – Immunogenicity Population

Figure 35: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seropositive Subjects – Per Protocol Population

Figure 36 Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects – Immunogenicity Population

Figure 37: Reverse Cumulative Distribution of ZIKV ELISA by Time Point and Treatment Group – Baseline ZIKV Seronegative and DENV Seronegative Subjects – Per Protocol Population

GMT

Figure 38: Geometric Mean ZIKV ELISA Titer (GMT) by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

Figure 39: Geometric Mean ZIKV ELISA Titer (GMT) by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

Seropositivity, Threshold ≥200

Figure 40: Percent of Subjects Seropositive at Threshold of ≥200 of ZIKV ELISA Assay by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

Figure 41: Percent of Subjects Seropositive at Threshold of ≥200 of ZIKV ELISA Assay by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

Seropositivity, Threshold ≥600

Figure 42: Percent of Subjects Seropositive at Threshold of ≥600 of ZIKV ELISA Assay by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

Figure 43: Percent of Subjects Seropositive at Threshold of ≥600 of ZIKV ELISA Assay by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

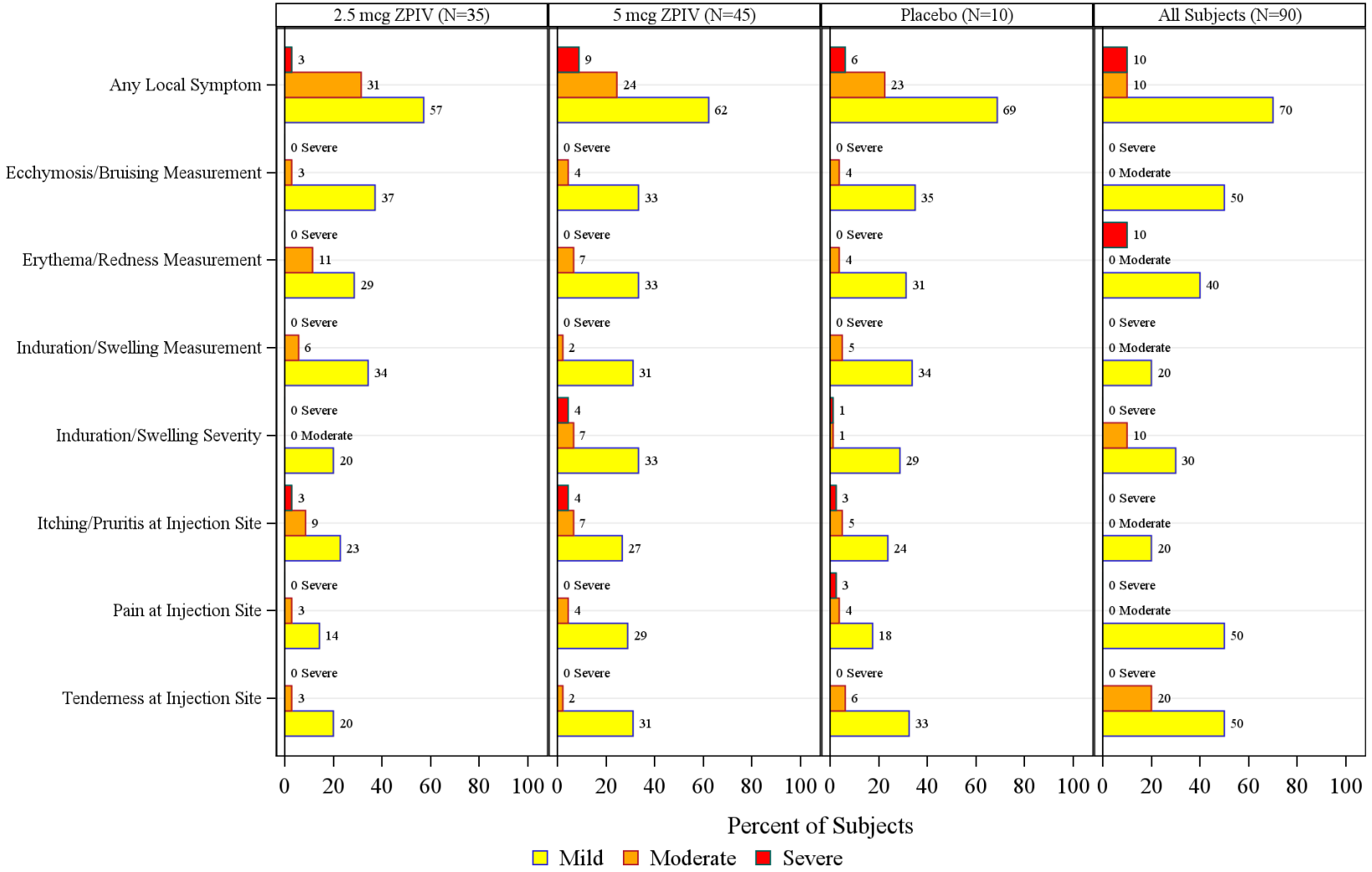
Seroconversion

Figure 44: Percent Seroconversion (≥4-Fold Rise from Baseline) of ZIKV ELISA Assay by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Immunogenicity Population

Figure 45: Percent Seroconversion (≥4-Fold Rise from Baseline) of ZIKV ELISA Assay by Baseline Flavivirus Immune Status, Time Point, and Treatment Group – Per Protocol Population

14.3.1.1 Solicited Adverse Events

Figure 46: Maximum Severity of Solicited Local Adverse Events by Symptom and Treatment Group – Post Any Dose

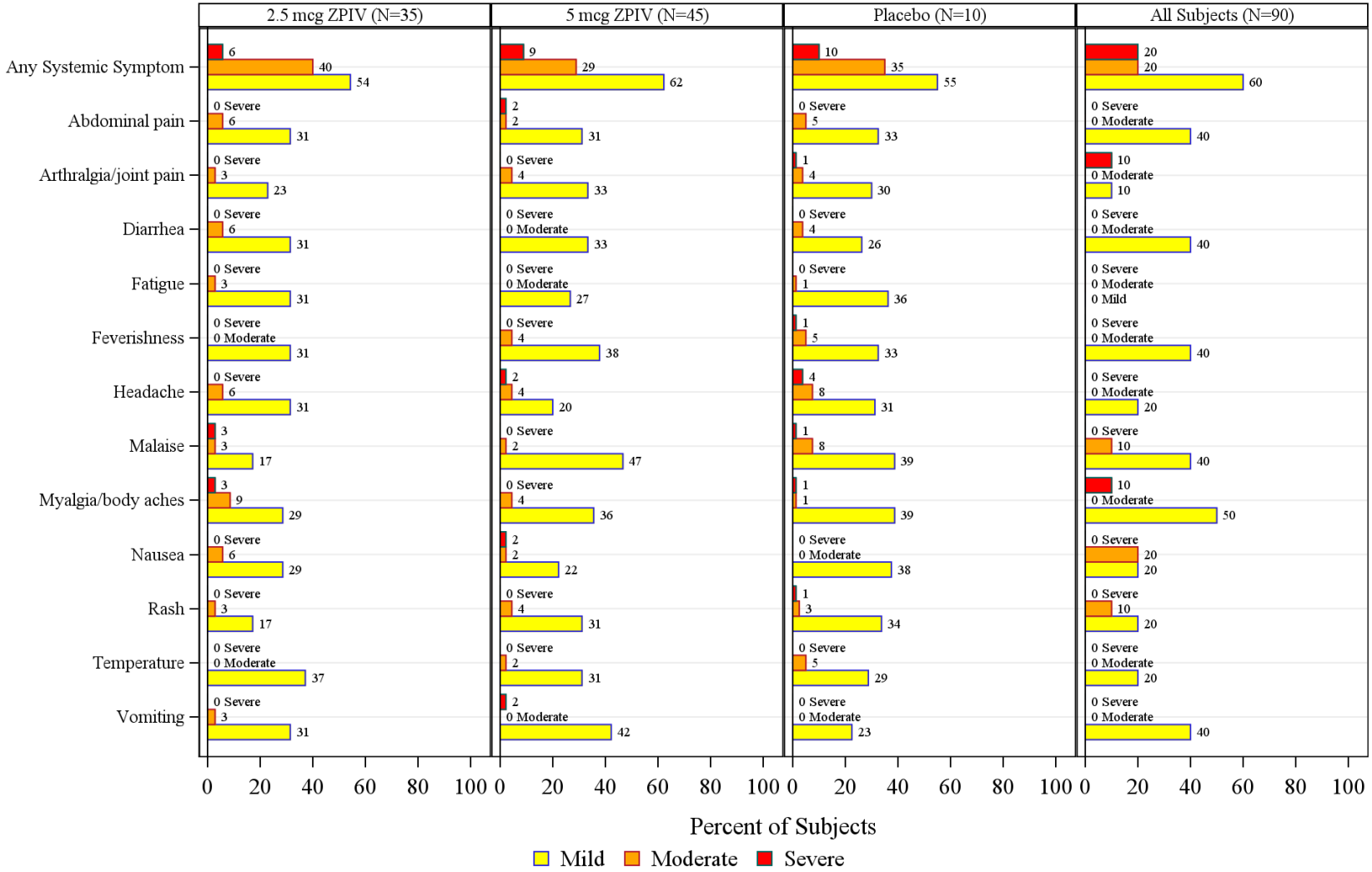


Figures with format similar to Figure 46:

Figure 47: Maximum Severity of Solicited Local Adverse Events by Symptom and Treatment Group – Post Dose 1

Figure 48: Maximum Severity of Solicited Local Adverse Events by Symptom and Treatment Group – Post Dose 2

Figure 49: Maximum Severity of Solicited Systemic Adverse Events by Symptom and Treatment Group – Post Any Dose

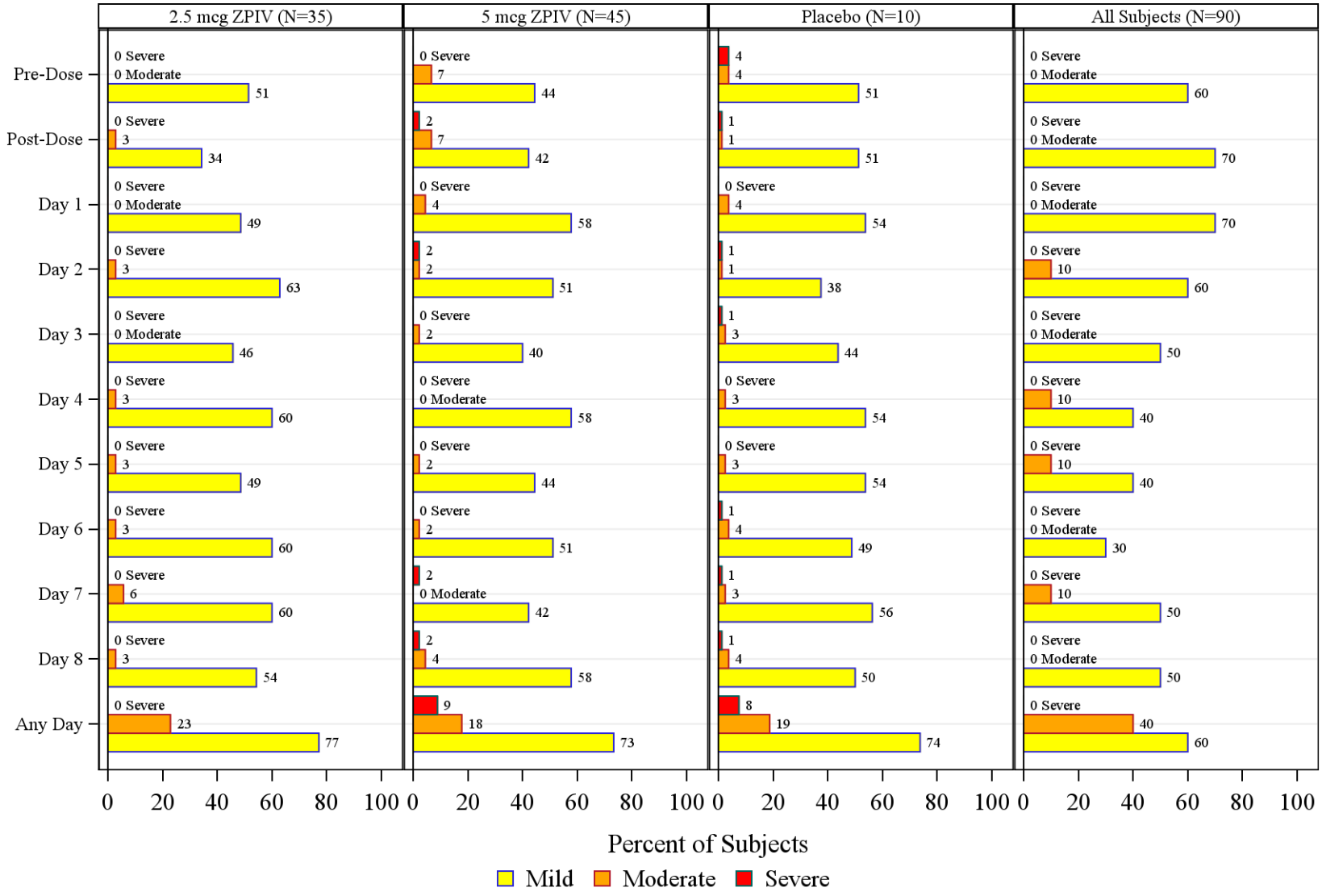


Figures with format similar to Figure 49:

Figure 50: Maximum Severity of Solicited Systemic Adverse Events by Symptom and Treatment Group – Post Dose 1

Figure 51: Maximum Severity of Solicited Systemic Adverse Events by Symptom and Treatment Group – Post Dose 2

Figure 52: Maximum Severity of Solicited Local Symptoms by Days Post Treatment and Treatment Group – Post Any Dose

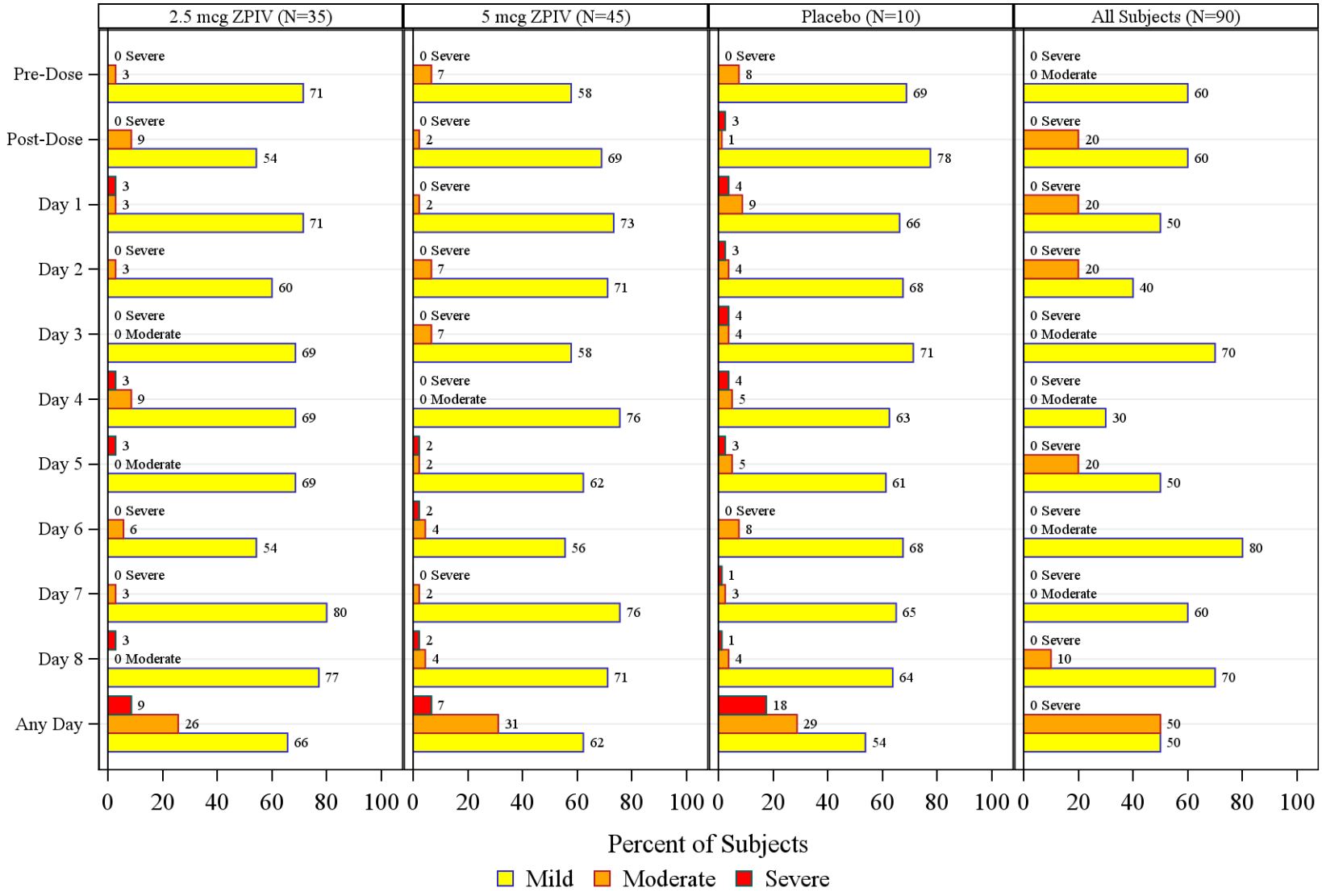


Figures with format similar to Figure 52:

Figure 53: Maximum Severity of Solicited Local Symptoms by Days Post Treatment and Treatment Group – Post Dose 1

Figure 54: Maximum Severity of Solicited Local Symptoms by Days Post Treatment and Treatment Group – Post Dose 2

Figure 55: Maximum Severity of Solicited Systemic Symptoms by Days Post Treatment and Treatment Group – Post Any Dose



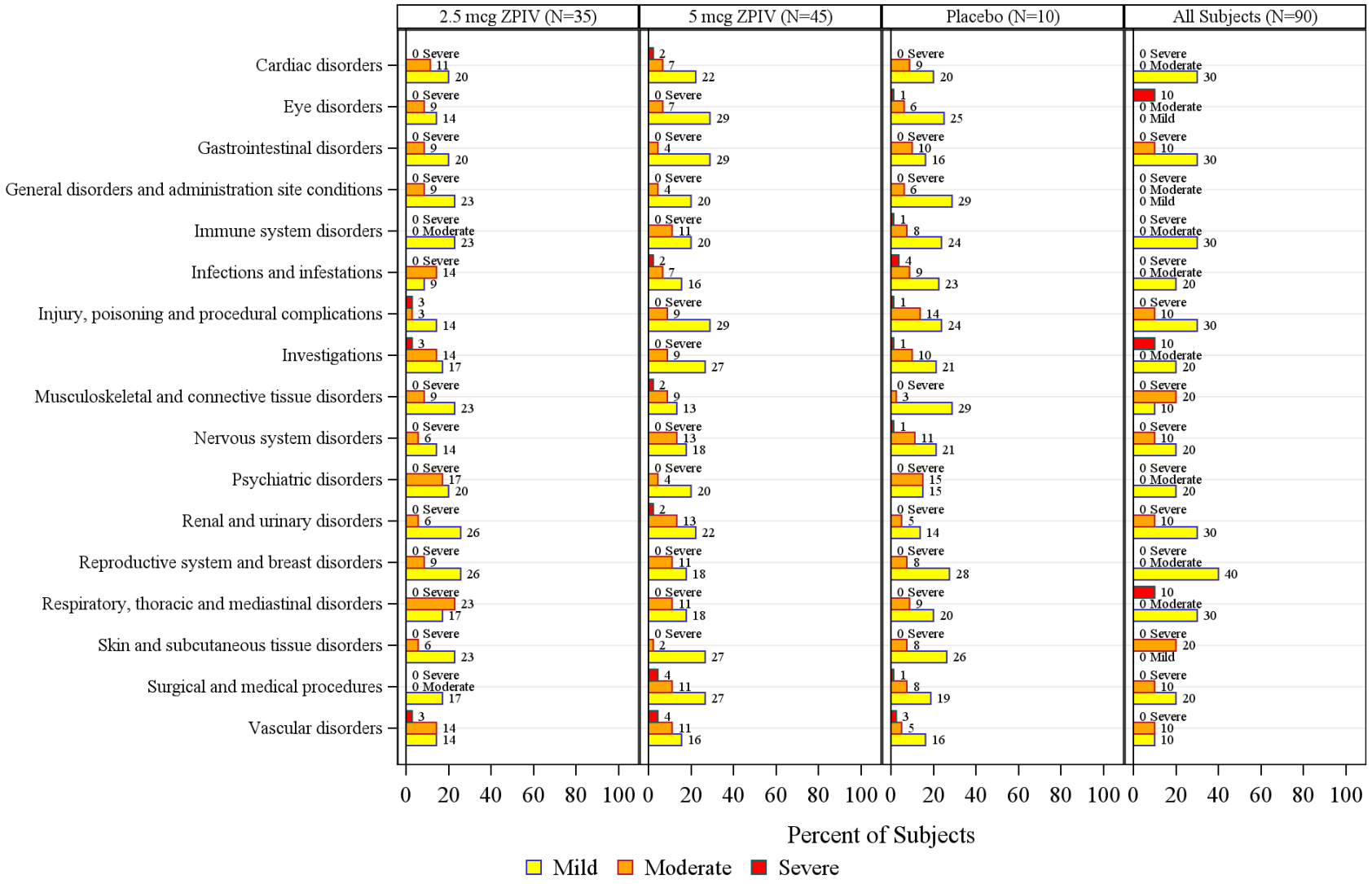
Figures with format similar to Figure 55:

Figure 56: Maximum Severity of Solicited Systemic Symptoms by Days Post Treatment and Treatment Group – Post Dose 1

Figure 57: Maximum Severity of Solicited Systemic Symptoms by Days Post Treatment and Treatment Group – Post Dose 2

14.3.1.2 Unsolicited Adverse Events

Figure 58: Frequency of Adverse Events by MedDRA System Organ Class, Treatment Group, and Severity – Post-Any Dose



Figures with similar format:

Figure 59: Frequency of Adverse Events by MedDRA System Organ Class, Treatment Group, and Severity – Post-Dose 1

Figure 60: Frequency of Adverse Events by MedDRA System Organ Class, Treatment Group, and Severity – Post- Dose 2

Figure 61: Frequency of Related Adverse Events by MedDRA System Organ Class, Treatment Group, and Severity – Post-Any Dose

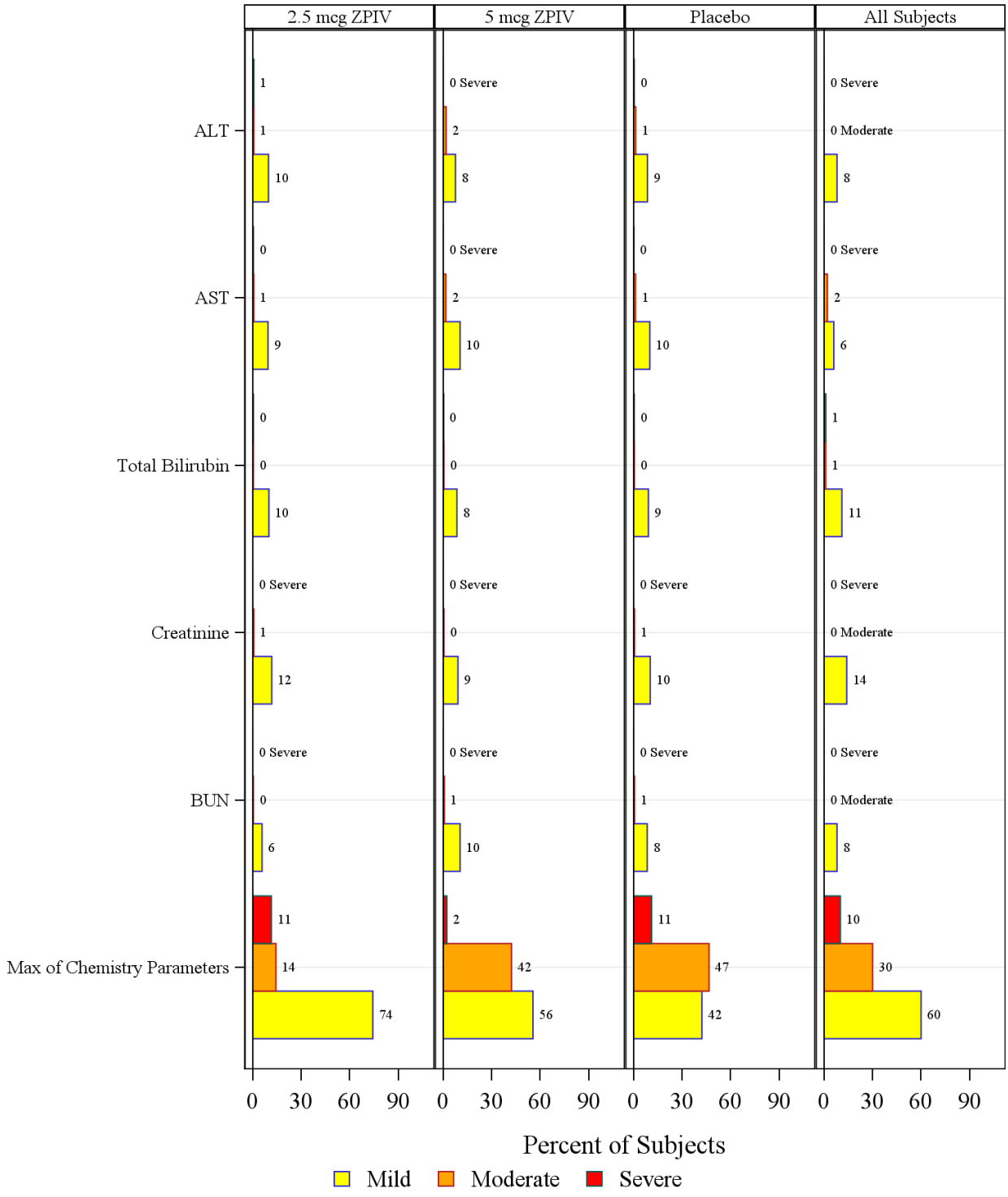
Figure 62: Frequency of Related Adverse Events by MedDRA System Organ Class, Treatment Group, and Severity – Post-Dose 1

Figure 63: Frequency of Related Adverse Events by MedDRA System Organ Class, Treatment Group, and Severity – Post- Dose 2

14.3.5 Displays of Laboratory Results

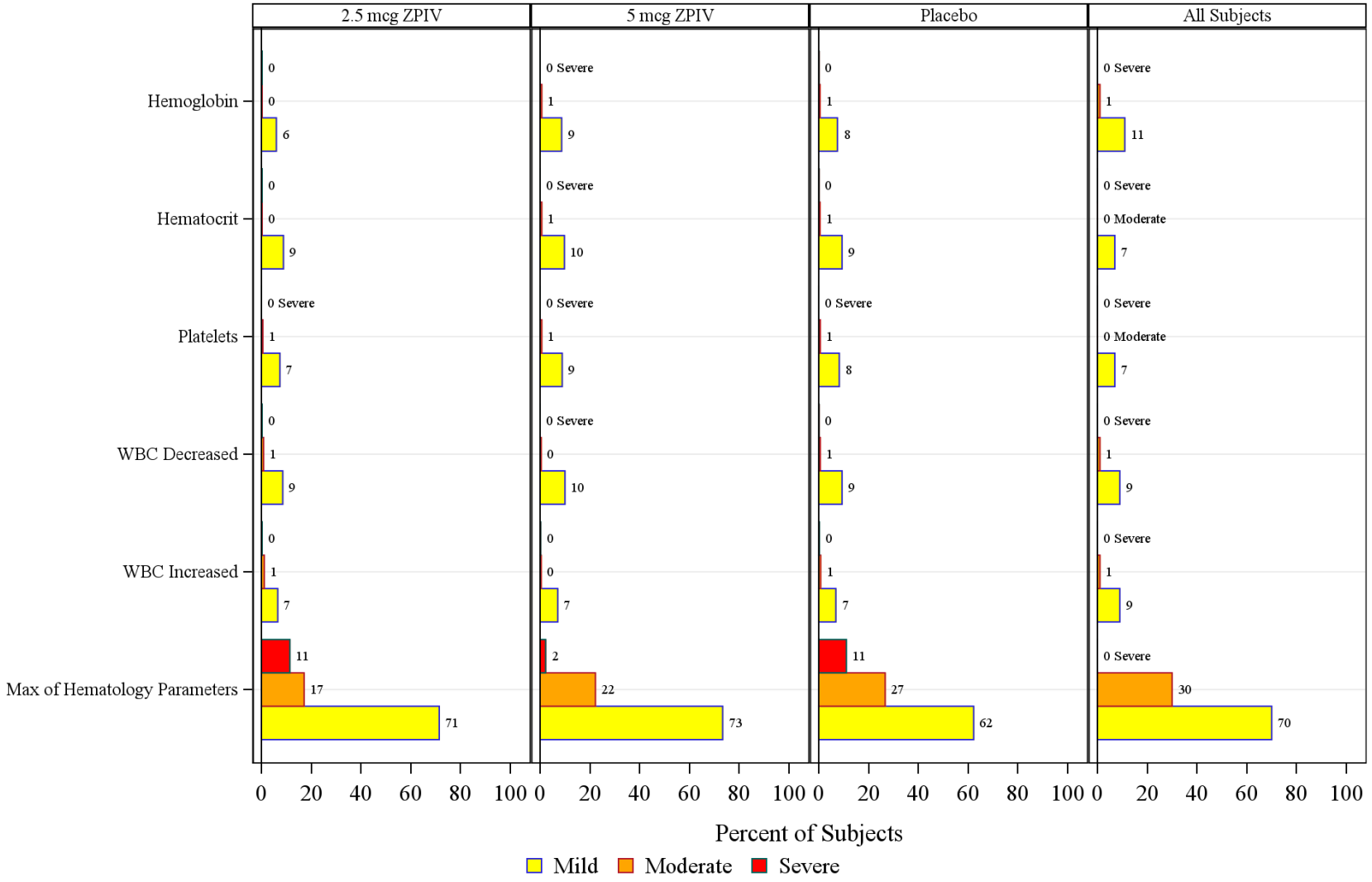
14.3.5.1 Chemistry Results

Figure 64: Clinical Laboratory Results by Maximum Severity and Treatment Group – Chemistry



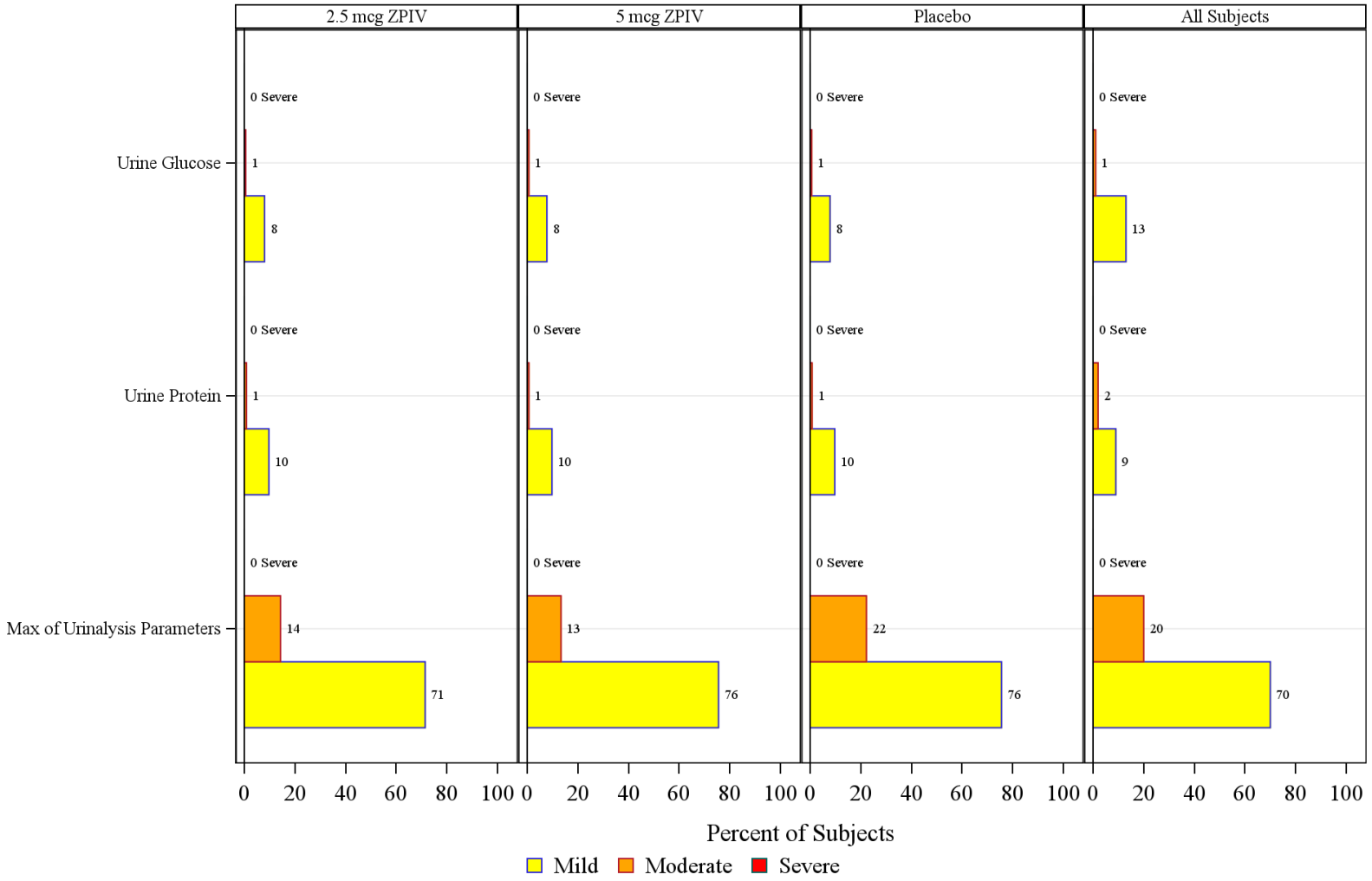
14.3.5.2 Hematology Results

Figure 65: Clinical Laboratory Results by Maximum Severity and Treatment Group – Hematology



14.3.5.3 Urinalysis Results

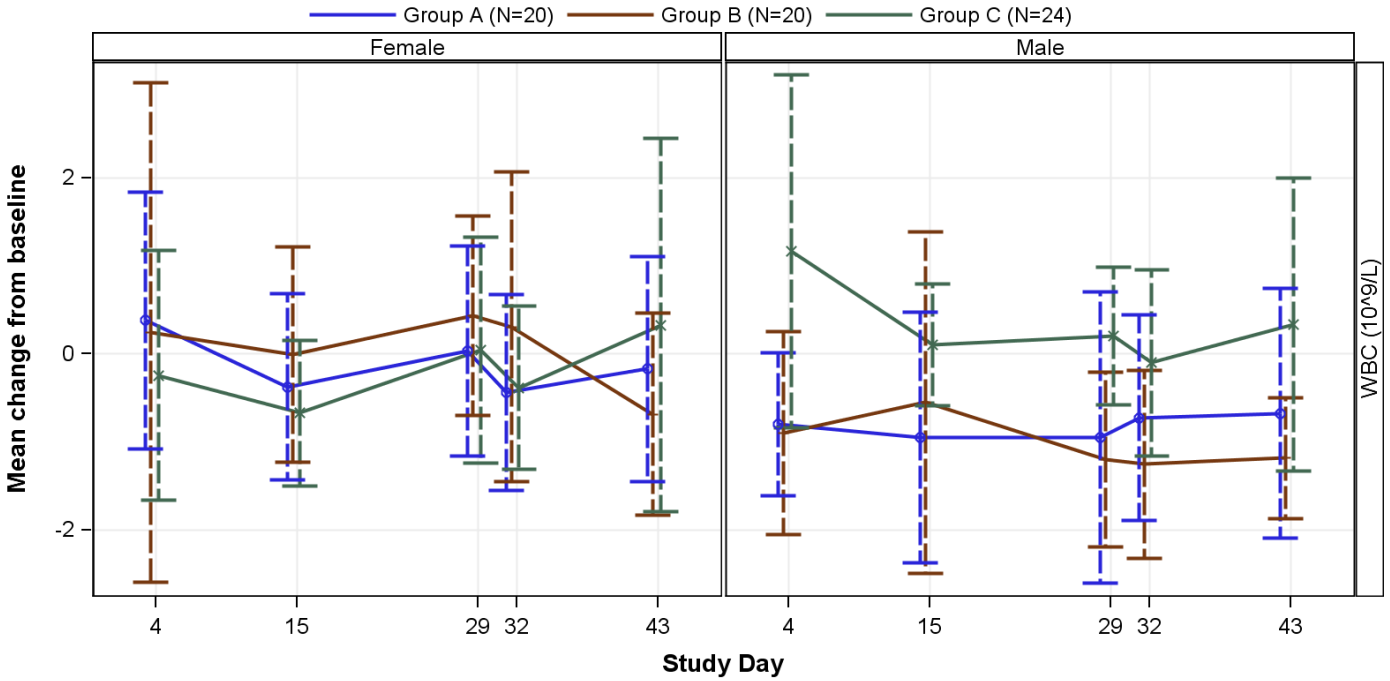
Figure 66: Clinical Laboratory Results by Maximum Severity and Treatment Group – Urinalysis



14.3.5 Displays of Laboratory Results

Figure 67: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – ALT

[Implementation note: the figure below is just an example. There will a single panel and individual curves for 2.5 mcg ZPIV, 5 mcg ZPIV and Placebo groups. The x-axis will have Day 8, Day 15, Day 36, and Day 43. Separate panels for male and female subjects will be generated for parameters graded separately by sex.]



The bars represent the upper and lower limits of the 95% confidence interval for mean change from baseline.

Figures with similar format:

Figure 68: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – AST

Figure 69: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – Total Bilirubin

Figure 70: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – BUN

Figure 71: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – Creatinine

Figure 72: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – WBC

Figure 73: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – Hemoglobin

Figure 74: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – Hematocrit

Figure 75: Laboratory Results by Time Point: Mean Changes from Baseline by Treatment Group – Platelet Count

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **Listing of Subjects Receiving Investigational Product**

[Placeholder for the CSR]

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: Early Terminations or Discontinued Subjects

[Implementation note: Listing will be sorted by Treatment Group, Subject ID, alphabetically by Category.]

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: Subject-Specific Protocol Deviations

[Implementation note: Listing will be sorted by Treatment Group, Subject ID, DV number.]

Treatment Group	Subject ID	Deviation 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 4: Non-Subject-Specific Protocol Deviations

[Implementation note: Listing will be sorted by DV number.]

Deviation Number	Deviation	Deviation Category	Start Date	End Date	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Immunogenicity Analysis

Listing 5: Subjects Excluded from Analysis Populations

[Implementation note: Listing will be sorted by Treatment Group, Subject ID]

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]		
"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.					

16.2.4 Demographic Data

Listing 6: Demographic Data

[Implementation note: If a subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)." The 'Seropositive Flaviviruses at Baseline' will list all flaviviruses that the subject was seropositive to at baseline, or 'None' if none. Listing will be sorted by Treatment Group then Subject ID.]

Treatment Group	Subject ID	Age at Enrollment (years)	BMI at Screening (kg/m^2)	Sex	Ethnicity	Race	Seropositive Flaviviruses at Baseline

Listing 7: Pre-Existing and Concurrent Medical Conditions

[Implementation note: Listing will be sorted by Treatment Group, Subject ID, MH number.]

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.6 Individual Immunogenicity Response Data

Listing 8: Individual Immunogenicity Response Data

[Implementation note: Listing will be sorted by Treatment Group, Subject ID, Planned Time Point. The 'Seropositive Flaviviruses at Baseline' will list all flaviviruses that the subject was seropositive to at baseline, or 'None' if none.]

Treatment Group	Subject ID	Seropositive Flaviviruses at Baseline	Planned Time Point	Actual Study Day	ZIKV MN50 Titer	ZIKV ELISA Titer	DENV MN50 Titer

16.2.7 Adverse Events

16.2.7.1 Solicited Events

Listing 9: Solicited Events – Systemic Symptoms

[Implementation note: Listing will be sorted by Treatment Group, Subject ID, Dose Number, Post Dose Day, Symptom.]

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?[b]	Alternate Etiology
				MA				
				Clinic				

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
[b] Grade 3 events only.
Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 10: Solicited Events – Local Symptoms

[Implementation note: Listing will be sorted by Treatment Group, Subject ID, Dose Number, Post Dose Day, Symptom.]

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity
				MA		
				Clinic		

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

16.2.7.2 Unsolicited Events

Listing 11: Unsolicited Adverse Events

[Implementation note: This listing includes all unsolicited adverse events. If the event is ongoing, indicate "ongoing" in the Duration column. Listing will be sorted by Treatment Group, Subject ID, Associated with Dose No., No. of Days Post Associated Dose.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											
For additional details about SAEs, see the table titled 'Listing of Serious Adverse Events'.											

Listing 12: Listing of Subject Information for Subjects Reporting ARI or AFI

[Implementation note: Columns indicating a 4-fold rise in neutralization titers will be either 'No' or 'Yes; [Day X, Day Y]']

Adverse Event	Illness Start Date (Study Day)	Associated with Dose #	# of Days Post Associated Dose	Blood ZIKV qT-PCR Result	Urine ZIKV qT-PCR Result	Blood DENV qT-PCR Result	Blood CHIKV qT-PCR Result	Last Immunogenicity Visit Prior to the Illness Visit (Study Day)	First Immunogenicity Visit Following the Illness Visit (Study Day)	4-fold rise in Blood ZIKV Titers After Illness Visit?	4-fold rise in Blood DENV Titers After Illness Visit?
Treatment Group: , Subject ID: , AE Number:											
Comments:											

Listing 13: Listing of Medical Treatment Sought for Subjects Reporting ARI or AFI

[Implementation note: "ZIKV or DENV Infection Confirmation Results" will have a format such as 'No/Yes; PCR positive (Day X)/Yes; 4-fold rise in [DENV/ZIKV] titers (Day Y to Day Z)/Yes; PCR positive (Day X), 4-fold rise in [ZIKV/DENV] titers (Day Y, Day Z)]

Treatment Group	Subject ID	Illness Number	Study Day	ZIKV or DENV Infection Confirmation	Medical Facility	Date Treatment Sought	Outcome

Listing 14: Listing of AFI/ARI Symptoms Reported in Subjects Experiencing ARI or AFI

[Implementation Note: Listing will be sorted by Treatment Group, Subject ID, and Illness Number.

"ZIKV or DENV Infection Confirmation" will have a format such as 'No/Yes; PCR positive (Day X)/Yes; 4-fold rise in [DENV/ZIKV] titers (Day Y, Day Z)/Yes; PCR positive (Day X), 4-fold rise in [ZIKV/DENV] titers (Day Y to Day Z)]

Treatment Group	Subject ID	Illness Number	Study Day	ZIKV or DENV Infection Confirmation	Symptom	Severity	Start Day	Duration (Days)	Required Concomitant Medication?

Listing 15: Listing of Vital Signs in Subjects Reporting ARI or AFI

[Implementation Note: Listing will be sorted by Treatment Group, Subject ID, and Illness Number.

"ZIKV or DENV Infection Confirmation" will have a format such as 'No/Yes; PCR positive (Day X)/Yes; 4-fold rise in [DENV/ZIKV] titers (Day Y, Day Z)/Yes; PCR positive (Day X), 4-fold rise in [ZIKV/DENV] titers (Day Y to Day Z)]

Treatment Group	Subject ID	Illness Number	Study Day	ZIKV or DENV Infection Confirmation	Temperature (C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Weight (kg)	Height (cm)	BMI (kg/m^2)

Listing 16: Listing of Laboratory Results in Subjects Reporting ARI or AFI

[Implementation Note: Listing will be sorted by Treatment Group, Subject ID, and Illness Number.

"ZIKV or DENV Infection Confirmation" will have a format such as 'No/Yes; PCR positive (Day X)/Yes; 4-fold rise in [DENV/ZIKV] titers (Day Y, Day Z)/Yes; PCR positive (Day X), 4-fold rise in [ZIKV/DENV] titers (Day Y to Day Z)]

Treatment Group	Subject ID	Sex	Age	Illness Number	Study Day	ZIKV or DENV Infection Confirmation Results	Lab Test	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

16.2.8 Individual Laboratory Measurements

Listing 17: Clinical Laboratory Results – Chemistry

[Implementation Note: Listing will be sorted by Treatment Group, Subject ID, and Planned Time Point]

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 18: Clinical Laboratory Results – Hematology

[Implementation Note: Listing will be sorted by Treatment Group, Subject ID, and Planned Time Point]

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 19: Clinical Laboratory Results – Urinalysis

[Implementation Note: Listing will be sorted by Treatment Group, Subject ID, and Planned Time Point]

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)

16.2.9 Vital Signs and Physical Exam Findings

Listing 20: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled. The severity should be included in parentheses after the result for abnormal assessments. The listing will be sorted by Treatment Group, Subject ID, and Planned Time Point]

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)	BMI (kg/m^2)

Listing 21: Physical Exam Findings

[Implementation Note: This listing includes all physical exam findings, scheduled and unscheduled. If a subject does not have any findings upon examination, they will not be included in this listing. If reported as an AE, display "Yes" with the AE Number in parentheses, e.g., "Yes (7)". The listing will be sorted by Treatment Group, Subject ID, Planned Time Point.]

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

Listing 22: Concomitant Medications

[Implementation Note: If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Number in parentheses, e.g., "Yes (7)". The listing will be sorted by Treatment Group, Subject ID, and CM Number.]

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for ARI/AFI?	Taken for ZIKV or DENV Infection?	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.8.6 Pregnancy Reports

Listing 23: Pregnancy Reports – Maternal Information

[Implementation Note: Only include the "Pregnancy Number" column if a subject has more than 1 pregnancy. Date of Conception will be calculated based on estimated delivery date. BMI will be calculated based on pre-pregnancy height and weight. Mother's weight gain will be calculated based on pre-pregnancy weight and end of pregnancy weight. If a major congenital anomaly with previous pregnancy, display "Yes" and the text from the "specify" field, separated by a colon. If any substance use is reported, include a listing of substance use. If autopsy revealed an alternate etiology, display "Yes" and the text from the "specify" field, separated by a colon. If abnormality in product of conception, display "Yes" and the text from the "specify" field, separated by a colon. Sort order: Treatment Group, Subject ID, Pregnancy Number.]

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 24: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[a]	Late TB[a]	Post TB[a]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?
Gravida includes the current pregnancy, para events do not.															
[a] Preterm Birth [a] Term Birth															

Listing 25: Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Congenital Anomalies are included in the Adverse Event listing.												

Listing 26: Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 27: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion