CLINICAL STUDY PROTOCOL

A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF mRNA-1325 ZIKA VACCINE IN HEALTHY ADULTS IN A NON-ENDEMIC ZIKA REGION

PROTOCOL NO. mRNA-1325-P101

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Version of Protocol: Final 6.0

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CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Signature Page

PROTOCOL TITLE: A Phase 1, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of mRNA-1325 Zika Vaccine in Healthy Adults in a Non-endemic Zika Region

PROTOCOL NUMBER: mRNA-1325-P101

PPD

PPD Moderna Therapeutics

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Date

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Date

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Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "A Phase 1 Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of mRNA-1325 Zika Vaccine in Healthy Adults in a Non-endemic Zika Region" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Signature of Investigator	Date

Printed Name of Investigator

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Protocol Synopsis

Protocol Number:	**mRNA-1325-P101**
Title:	A Phase 1, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Immunogenicity of mRNA-1325 Zika Vaccine in Healthy Adults in a Non-endemic Zika Region
Study Phase:	1
Study Sites:	At least 2 sites in the United States or its territories
Objectives:	Primary: • To assess the safety of a 2-dose vaccination schedule of mRNA-1325 Zika vaccine, given 28 days apart, across a range of dose levels in flavivirus-seronegative and flavivirus-seropositive subjects compared with placebo. Secondary: • To assess the immunogenicity of a range of doses of mRNA-1325 Zika vaccine and to select a dose to move forward into further development, based on changes from Baseline in the following tests: • Zika virus (ZikaV)-specific neutralizing antibody titers measured by a Plaque Reduction Neutralizing Titer EC50 (PRNT50); Exploratory: • ZikaV antigen-specific stimulation of T cells measured by interferon gamma (IFNγ) enzyme-linked ImmunoSpot (ELISPOT) on subject-derived peripheral blood mononuclear cells (PBMCs), if results of interim immunogenicity analyses warrant further analyses of samples. • To assess the impact of mRNA-1325 Zika vaccine on a range of other functional and diagnostic flavivirus assays.
Study Design and Methodology:	This is a Phase 1, double-blind, placebo-controlled, dose-finding study to evaluate the safety and immunogenicity of a range of dose levels of mRNA-1325 Zika vaccine given in a 2-dose vaccination schedule, 28 days apart, and compared with placebo in healthy adult subjects (18 to 49 years of age, inclusive). mRNA-1325 is an mRNA-based vaccine candidate being tested for its ability to safely induce an immune response expected to be able to prevent ZikaV infection. ZikaV is a single-stranded RNA flavivirus, which is transmitted to humans by a mosquito vector (mainly *Aedes aegypti* but other *Aedes* mosquitoes are believed to be competent vectors) or by person-to-person spread, mainly through sexual transmission.

Currently there is no vaccine to protect against this disease, which has spread rapidly from Asia to most tropical and subtropical regions including the Americas.

This is a 2-part study. Part A includes dose-finding, safety, and immune testing through 28 days following the second vaccination. Once subjects complete the final visit in Part A, they will be entered into Part B. Part B is a blinded follow-up period with assessment of safety through 12 months and immune persistence at 168 (±15) days and 364 (+15) days following the second vaccination in Part A. Immune persistence at 168 days and 364 days will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence.

Part A

Subjects will be randomly assigned in a blinded fashion in an approximate 4:1 ratio to receive mRNA-1325 or placebo at 1 of 3 dose levels (10 µg, 25 µg, or 100 µg), with each subject receiving 2 vaccinations separated by 28 (+7) days. Dosing will begin with 10 µg (Cohort 2), followed by 25 µg (Cohort 3), and then 100 µg (Cohort 4). There will be no Cohort 1 included in this study. Approximately two-thirds of the enrolled subjects at each dose level will be flavivirus naïve and approximately one-third will be flavivirus seropositive as a result of having received a yellow fever vaccination in the past 20 years by either: a) military assignment in the previous 20 years that requires a yellow fever vaccination; or 2) yellow fever vaccination documented on an international certificate or other confirmatory documentation of yellow fever vaccination.

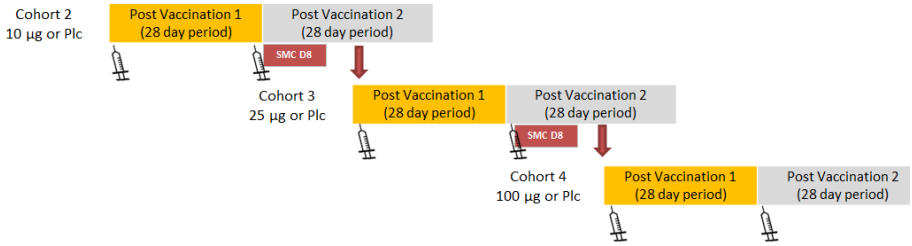
Cohort and Treatment Assignment

Cohort	Flavivirus Status	Treatment Assignment (µg mRNA-1325 or placebo)	Total (Ratio)
2	+	10	30 (4:1)
	-	10	
	+	placebo	
	-	placebo	
3	+	25	30 (4:1)
	-	25	
	+	placebo	
	-	placebo	
4	+	100	30 (4:1)
	-	100	
	+	placebo	
	-	placebo	

Abbreviations: +, flavivirus seropositive; -, flavivirus seronegative.

For each cohort, a sentinel safety group will enroll 3 flavivirus-seronegative subjects randomized to mRNA-1325 and followed for 7 days after first vaccination, with review of reactogenicity (Section 3.5.6) and safety laboratory results, prior to randomizing the remainder of the cohort. An internal safety team (IST) will oversee the safety of the trial and will review blinded safety data during Part A of the study to ensure adherence to the protocol, monitor safety laboratory test results and reactogenicity, and raise concerns to the Safety Monitoring Committee (SMC) should there be safety issues or operational challenges that could affect subject safety. Only after review by the IST of the blinded safety data (reactogenicity, safety labs, and AEs) through 7 days following first vaccination of the sentinel safety lead-in for each cohort planned will approval be given to allow randomization of the remainder of that cohort. The SMC will approve escalation to the next higher dosing cohort after review of blinded safety data of the currently dosed cohort through 7 days following the second vaccination and any cumulative safety data of all cohorts as the trial advances. The SMC will also be convened (ad hoc meeting) if a pause rule is triggered.

Dosing Schema by Cohort



Abbreviations: D, day; Plc, placebo; SMC, safety monitoring committee.

Note: Yellow shading depicts safety follow-up of the first vaccination period and grey shading depicts safety follow-up of the second vaccination period for cohorts by dose sequence.

Note: The SMC will approve escalation to the next higher dosing cohort after review of blinded safety data of the currently dosed cohort through 7 days following the second vaccination and any cumulative safety data of all cohorts as the trial advances.

The vaccine will be administered as an intramuscular (IM) injection (0.5 mL) into the deltoid muscle as a 2-dose vaccination schedule at Visits 1 and 4 (at least a 28-day interval between dosing). The second dose of study drug will be administered preferably in the same arm used for the first dose. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel, who will not participate in any other aspect of the study. The remainder of the site staff and all subjects will remain blinded to treatment assignment.

Screening and consent will occur over a 28-day period before randomization (West Nile virus serology screen can occur up to 90 days prior to randomization). A total of 30 subjects for each dose cohort will be assigned, 24 subjects to mRNA-1325 and 6 subjects to placebo (approximate 4:1 ratio overall). The first 3 subjects for each dose level will be randomized to mRNA-1325. Subjects who meet all eligibility criteria will receive the first vaccination at Visit 1. Of note, a subject who has met all eligibility criteria but is noted to have a blood pressure, heart rate or respiratory rate that is Grade 2 or greater (even after relaxing/resting) in the clinic on the day of vaccination should not receive a vaccination on that day and will need to return on a subsequent day for their vaccination. Similarly, if a subject has a fever (>37.9°C) or an intercurrent illness, vaccination should be withheld until resolved (as specified in exclusion criterion 20). Each subject will be monitored in the clinic for at least 1 hour following vaccination to assess for immediate reactogenicity, with vital sign measurements and local and systemic reactogenicity toxicity scored at that time. The highest toxicity recording will be entered into the electronic case report form.

Subjects will be instructed on recording reactogenicity, adverse events (AEs), and medications (prescription or over-the-counter) on the memory aid (ie, diary card), and will be provided measuring tools, and instructed to call or return to the clinic within 24 hours if a reactogenicity score reaches Grade 3 or greater during the first 7 days following vaccination. As standard practice, a reminder call will be made to the subject by the site at least once during the first 7 days following each vaccination to answer any questions and ensure that the memory aid is being completed correctly and consistently. All subjects will return on 7 (+3) (cellular PBMC testing) and 28 (+7) (humoral neutralization testing) days following each vaccination for safety assessments and blood sampling for immune testing.

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity) events (first 7 days after each vaccination); clinical laboratory test results including hematology, serum chemistry, coagulation, and urinalysis; vital sign measurements; and physical examination findings (Day 7 after each vaccination) and unsolicited AEs (throughout Part A). All unsolicited AEs and concomitant medication (including over the counter) usage will be collected. Specific categories of safety data collected will include serious adverse events (SAEs), AEs of special interest (AESIs), AEs leading to study withdrawal, and medically attended AEs. At clinic visits, the investigator will review, confirm, and grade the

reactogenicity recorded in the memory aid and inquire about and review AEs and medications.

All safety laboratory tests will be performed according to Table 6-1. Safety laboratory tests will be performed during Screening (to allow for assessment of inclusion and exclusion criteria), on the day of first vaccination (Visit 1), 7 (+3) days following each vaccination (Visit 2 and Visit 5), and 28 (+7) days following each vaccination (Visit 4 [prior to second vaccination] and Visit 7). At 17 (±3) days following each vaccination (Visit 3 and Visit 6) and at 21 (+3) days after the first vaccination (Visit 3a) for the sentinel subjects, a subset of safety laboratory tests will be performed as specified in Table 6-1. Blood test results (pre-vaccination) at Visit 1 will be the basis for evaluation of changes from Baseline after vaccination.

Blood samples for immunogenicity assessments (cellular and humoral) will be collected the day of vaccination (before vaccination) and 7 (+3) and 28 (+7) days, respectively, following each vaccination. Subjects that miss the second vaccination due to noncompliance with the visit schedule and not due to a cohort pause will still be required to follow the original visit and testing schedule. These subjects will be asked to undergo blood collection to comply with a second immune test at Visit 7 (56+7 days after first vaccination).

To allow cohort advancement, the following data from the highest dosed cohort is expected to be reviewed by the SMC: 1) toxicity scoring of safety laboratory test results through 7 days following the second vaccination (through Visit 5); 2) toxicity scoring of vital signs and reactogenicity through 7 days following the first and second vaccination (through Visit 5); 3) all unsolicited AEs (with grading and relatedness). Data will be prepared by dose category and timing relative to the last vaccination. As safety data on all cohorts accumulate, the SMC will also review ongoing AEs as well as cumulative safety laboratory test results, reactogenicity, and AEs across vaccine doses for subjects remaining in Part A of the study, thereby providing a cumulative and comprehensive review of safety. Should a cohort pause occur due to pre-specified criteria, the SMC will be convened for an unscheduled (ad hoc) meeting and be provided with specific safety data related to the trigger of the pause.

Part A is concluded for each subject at the time when they return to the clinic for Visit 7 (28 days following the second vaccination). At that time, a subject will be entered into Part B of the study. Once query resolution and immune testing is completed for each cohort in Part A, the database will be locked. Results will be provided to the Sponsor, SMC, and IST. The Sponsor may determine whether dosing

adjustments are required during the conduct of the study based on either safety or immune responses per cohort. As dose escalation occurs, cumulative analyses will be included for each subsequent data lock to allow for all prior dosing cohorts to be analyzed by cohort, treatment assignment, and in aggregate for mRNA-1325 exposure. Subject-level individual treatment assignment will not be released to the subjects or to those individuals involved in managing or assessing safety in Part B of the study until that portion of the study is completed.

Part B – 12 Month Follow-up After Final Vaccination

To monitor for longer-term safety and immune persistence, each subject will be entered into a continued blinded follow-up period (Part B). This period will be conducted such that subjects, observers, and safety monitors will remain blinded to treatment assignment. Part B of the study is initiated for a subject once they have returned for Visit 7 (28 days following the second vaccination). The safety database utilized for Part B may be accessed by the pharmacovigilance safety team for safety signal detection at scheduled intervals for ongoing assessments for a given vaccine candidate as well as for the mRNA platform technology.

Once entered into Part B, each safety contact will occur by telemedicine (eg, telephone, text message, internet) every 28 (±7) days, and blood samples for immune persistence will be collected from each subject at 168 (±15) days and 364 (+15) days following the second vaccination. Immune persistence at 168 days and 364 days will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence. Each safety contact will capture outcomes of any AESI or SAE that remains unresolved since the last visit or is newly identified through scripted query. The telemedicine visits may require additional data through medically attended visits, in addition to medications and vaccination taken by the subject during this time. Subjects will have consented during study enrollment to allow access to additional medical records needed to complete Part B, thereby allowing the blinding of the treatment assignment to be maintained.

When all subjects have completed their final contact (approximately 12 months after their last vaccination), immune testing is completed, and all queries resolved, the database will be locked and analyzed with a final clinical study report provided to regulators.

Inclusion Criteria: Each subject must meet all of the following criteria during the screening period to be enrolled in this study:

1. The subject is male or female between 18 and 49 years of age, inclusive.
2. The subject has a body mass index between 18 and 35 kg/m^2, inclusive.
3. The subject is considered by the investigator to be in good general health as determined by medical history.
4. Female subjects must be non-pregnant and non-lactating and meet one of the following criteria: a) post-menopausal (defined as 12 consecutive months with no menses without an alternative medical cause or documented plasma follicle-stimulating hormone level in the post-menopausal range); b) surgically sterile (ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). NOTE: these procedures and laboratory test results must be confirmed by physical examination or official written confirmation of a procedure; c) if of childbearing potential (defined as any female who has experienced menarche and who is NOT permanently sterile or post-menopausal), agrees to be heterosexually inactive from at least 21 days prior to enrollment and through 3 months after the final vaccination or agrees to consistently use any of the following methods of contraception from at least 21 days prior to enrollment and through 3 months after the final vaccination: condoms (male or female) with spermicide, diaphragm with spermicide, cervical cap with spermicide, intrauterine device, oral or patch contraceptives, Norplant®, Depo-Provera®, or other Food and Drug Administration (FDA)-approved contraceptive method that is designed to protect against pregnancy. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects must use an acceptable method of birth control (see above) and must also agree to refrain from donation of sperm from the time of first vaccination until 3 months following the last vaccination. Periodic abstinence, declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
5. Subject assigned to the flavivirus seropositive group has received a yellow fever vaccination in the past 20 years by either: a) military assignment in the previous 20 years that requires a yellow fever

vaccination; or 2) yellow fever vaccination documented on an international certificate or other confirmatory documentation.

6. The subject understands and agrees to comply with the study procedures and provides written informed consent.
7. The subject has access to a consistent and reliable means of telephone contact, which may be in the home, workplace, or by personal mobile electronic device.
8. The subject agrees to stay in contact with the study site for the duration of the study, to provide updated contact information as necessary, and has no current plans to move from the study area for the duration of the study.

Exclusion criteria: Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has any ongoing significant chronic illness requiring medical or surgical care. Asymptomatic conditions or findings (eg, mild hypertension, dyslipidemia) that are not associated with evidence of end-organ damage are not exclusionary provided that they are being appropriately managed and are clinically stable in the opinion of the investigator (ie, unlikely to result in symptomatic illness within the time-course of this study).
2. The subject has a history of active cancer (malignancy) in the last 10 years (exception is subjects with adequately treated non-melanomatous skin carcinoma, who may participate in the study).
3. The subject is a female of childbearing potential and has a positive pregnancy test at Screening or on the day of vaccination.
4. The subject has abnormal liver enzyme tests (increase in aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase) at Screening.
5. The subject has received another investigational product in another investigational study within 60 days, or 5 half-lives, whichever is longer, before the planned date of first vaccination.
6. The subject has received any live attenuated vaccines within 4 weeks before enrollment or inactive vaccines within 2 weeks before enrollment, or plans to receive any vaccine during the active vaccination period (through 4 weeks after their last planned vaccination).

7. The subject has received (at any time) a vaccine for Zika or dengue vaccine.
8. The subject has a history of confirmed Zika or dengue infection.
9. The subject has lived in or visited any Zika-endemic area (as defined by the World Health Organization [WHO; Appendix 4]) greater than 4 weeks in duration (flavivirus-seronegative group, only).
10. The subject has received any vaccination for a flavivirus (eg, yellow fever, Japanese encephalitis) in his or her lifetime (flavivirus-seronegative group, only), or received a vaccination for a flavivirus more than 20 years ago (flavivirus-seropositive group, only).
11. The subject has a positive West Nile virus antibody titer above the detection level of the assay (flavivirus-seronegative group, only). NOTE: West Nile virus titers are considered valid for a period of 90 days (allowing for the screening period on West Nile virus to exceed the standard 28 days as noted for all other screening parameters).
12. The subject has reported previously participating in an investigational study involving lipid nanoparticles.
13. The subject has a history of hypersensitivity or serious reactions (eg, anaphylaxis, urticaria, other significant reaction) to previous vaccinations.
14. The subject has any known or suspected autoimmune disease or immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination.
15. The subject has a history of inflammatory arthritis.
16. The subject has a neurologic disorder (eg, history of seizures, Guillain-Barré syndrome, dementia, vasculitis, or any known congenital or acquired disorder).
17. The subject has a history of febrile disease with arthritis or arthralgia within 2 weeks of dose administration.
18. The subject received immunoglobulins and/or any blood products within the 3 months preceding the administration of the study drug or plans to receive such products at any time during the study.
19. The subject has had chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune-modifying drug within 6 months before vaccine

administration or plans to receive any products during the active vaccination period (through 4 weeks after their last planned vaccination). An immunosuppressant dose of a glucocorticoid will be defined as a systemic dose of ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

20. The subject has any acute illness at the time of enrollment (defined as the presence of a moderate or severe illness with or without fever, or an oral body temperature >37.9°C on the planned day of vaccination). In such cases, subjects may be re-evaluated during the screening period for resolution of the illness to allow at least 3 days of wellness before the planned vaccination as long as they remain within the 28-day screening period.
21. The subject has any significant disorder of coagulation (acquired or hereditary) requiring ongoing or intermittent treatment. Subjects receiving prophylactic antiplatelet medications, eg, low-dose acetylsalicylic acid (≤100 mg/day or equivalent), and without clinically apparent bleeding tendency, are eligible.
22. The subject has a history of idiopathic urticaria.
23. The subject has a documented history of alcohol abuse or drug addiction within 1 year before the planned day of dose administration.
24. The subject has a positive test result for drugs of abuse at Screening or on the day of first vaccination.
25. The subject has any abnormality or permanent body art (eg, tattoo) that, in the opinion of the investigator, would obstruct the ability to observe local reactions at the injection site (deltoid region).
26. The subject has any condition that, in the opinion of the investigator, would pose a health risk to the subject if enrolled or could interfere with evaluation of the study drug or interpretation of study results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).
27. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies.
28. The subject has donated blood or blood products >450 mL within 30 days of dosing.

29. The subject has screening safety laboratory test results (urine and serum) outside the normal range of the laboratory and with a toxicity score with Grade 1 or higher.
30. The subject has screening vital sign of blood pressure, heart rate, or respiratory rate that is equal to or greater than Grade 1 by toxicity score.
31. The subject is an employee or first degree relative of the Sponsor, PPD, or study site personnel.

Note that some exclusion criteria are time-related. A subject may be re-evaluated on more than one occasion during the screening period to assess for resolution. There is allowance to repeat an abnormal vital sign measurement and Grade 1 laboratory abnormalities (except aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) once to allow for inclusion into the study and the last value measured will be used to allow inclusion in the study.

Part A Safety Assessments:

- Solicited AEs with toxicity scoring (local and systemic reactogenicity events) collected for 7 days following each vaccination
- Unsolicited AEs collected for 28 days following each vaccination; additional classification if serious, medically attended, leading to study withdrawal, or an AESI
- Safety laboratory test results with toxicity scoring (hematology, serum chemistry, and coagulation) collected at Baseline and 7 (+3) days and 28 (+7) days following each vaccination
- Urinalysis test results with toxicity scoring collected at Baseline and 7 (+3) days following each vaccination
- A subset of safety laboratory test results (as specified in Table 6-1) with toxicity scoring collected additionally at 17 (±3) days following each vaccination and 21 (+3) days (sentinel subjects) following the first vaccination
- Vital sign measurements with toxicity scoring on day of vaccination and 7 and 28 days following each vaccination

Part B Safety Assessments:

- AESIs and SAEs through 1 year (or until resolved, whichever occurs first) following the last vaccination

Part A Immunogenicity Testing:	• Neutralizing serum antibody titers (PRNT50) to Zika (Baseline [pre-vaccination at Visit 1] and at 28 days following each vaccination [Visits 4 and 7, respectively]) • Neutralizing serum antibody titers (PRNT50) to yellow fever (Baseline [pre-vaccination at Visit 1] and at 28 days following each vaccination [Visits 4 and 7, respectively]) in the flavivirus-seropositive group • T-cell response (cytokine activation to IFNγ or other cytokines) (Baseline [pre-vaccination at Visit 1] and at 7 days following each vaccination [Visits 2 and 5, respectively]), if results of interim immunogenicity analyses warrant further analyses of samples.
Part B Immunogenicity Testing:	• Neutralizing serum antibody titers (PRNT50) to Zika virus at 168 (±15) days and 364 (+15) days (Visits 12 and 19, respectively) following the second vaccination will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence.
Study Drug, Dosage, and Route of Administration:	10-, 25-, or 100-µg mRNA-1325 or placebo (0.9% Sodium Chloride Injection, USP or BP) will be prepared as outlined in the pharmacy manual and administered via IM injection (0.5 mL) into the deltoid muscle on designated vaccination days. The second dose of study drug will be administered preferably in the same arm used for the first dose.
Sample Size:	Approximately 90 subjects are planned to be randomly assigned to receive study treatment. Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and is considered sufficient to meet the study objectives of identifying a dose and establishing initial safety results in a population of healthy adults in a non-endemic Zika region.
Statistical Methods:	**Safety:** Data from subjects who received placebo will be pooled across cohorts for all treatments. Reactogenicity will be summarized by treatment assignment (10-, 25-, or 100-µg mRNA-1325 or placebo), vaccination (first or second), duration, and severity. Adverse events will be coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities and summarized by part, treatment assignment, vaccination (first or second), and overall. Adverse events will also be summarized by severity and relationship to the study vaccine. Descriptive statistics will be presented and the difference in the proportion of subjects with AEs will be provided comparing each dose level with placebo recipients across all groups. Individual subject

listings will be provided for all AEs, AEs leading to study withdrawal, AESIs, medically attended AEs, and SAEs.

Safety data from clinical laboratory test results and vital sign measurements will be graded by severity scoring and analyzed by treatment group and vaccination (first or second). Absolute and change from baseline values will be provided according to the toxicity table, along with mean, median, and standard deviation. Results of serology, urine drug screen, and pregnancy tests will be listed for all subjects randomly assigned to receive study treatment.

Medical history data for all subjects randomly assigned to receive study treatment will be presented by subject in a listing.

Baseline demographic and background variables will be summarized by treatment group and cohort for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

Prior and concomitant medication will be listed (with start and stop dates) for each subject and summarized by common medical dictionary coding. Any vaccinations that occur during the trial conduct will also be captured and summarized.

Immunogenicity: The following immunogenicity outcome measures (for serum neutralizing antibody titers) and their 95% CIs, where appropriate, will be summarized by treatment group and by visits after each vaccination:

- Geometric mean titer (GMT) of anti-Zika virus neutralizing antibodies (PRNT50 assay)
    - Part A: At Baseline (pre-vaccination at Visit 1) and on 28 days after both first and second vaccination (Visits 4 and 7, respectively)
    - Part B: At 168 (±15) days and 364 (+15) days (Visits 12 and 19, respectively) will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence.

- Geometric mean ratio (GMR)$_{Post/Pre}$
  - Part A and Part B: The ratio of post-vaccination GMT to pre-vaccination (Visit 1) GMT of subjects who have a baseline sample (pre-vaccination at Visit 1) and post-vaccination sample at any post-dose time point (Visits 4, 7, 12, or 19; data from visits 12 and 19 will be included only if based on interim immunogenicity analyses results the evaluation of these later timepoints is warranted.)
- Seroconversion
  - Part A: The proportion of subjects with Zika virus PRNT50 titer ≥1:10, ≥1:20, ≥1:40, ≥1:80, ≥1:160, and ≥1:320 at Baseline, Visit 4, and Visit 7
  - Part A: The proportion of subjects with baseline Zika virus PRNT50 titer <1:10 and post-vaccination Zika virus PRNT50 titer of ≥1:20; or with baseline Zika virus PRNT50 titer ≥1:10 and with post-vaccination 4-fold titer increase (Visits 4 or 7)
  - Part B: The proportion of subjects who maintained seroconversion status at specific time points of 168 (±15) days and 364 (+15) days (Visits 12 and 19, respectively). Data from visits 12 and 19 will be included only if based on interim immunogenicity analyses results the evaluation of these later timepoints is warranted.
- Cross-stimulation with prior flavivirus vaccination (subset of flavivirus-seropositive subjects)
  - Part A:
  - Geometric mean titer (GMT) of anti-yellow fever neutralizing antibodies at Baseline, Visit 4, and Visit 7
  - Geometric mean ratio (Post/Pre) of anti-yellow fever neutralizing antibodies at Visit 4 and Visit 7
  - The proportion of subjects with anti-yellow fever antibody titer ≥1:10, ≥1:20, ≥1:40, ≥1:80, ≥1:160, and ≥1:320 at Baseline, Visit 4, and Visit 7
  - Additional neutralization assays for other flavivirus may be performed in select subsets

Following completion of each cohort in Part A, the database will be locked for that cohort and safety and immune test results will be analyzed through 28 days following the second vaccination. As dose escalation occurs, cumulative analyses will be included for each

subsequent data lock to allow for all prior dosing cohorts to be analyzed by cohort, treatment assignment, and in aggregate for mRNA-1325 exposure. Immunogenicity and safety data, including mean group analyses of change from Baseline, where applicable, will be summarized for each dose cohort. These data are required to inform decisions on dose selection for this and other development programs using the same mRNA platform. Subject level treatment assignment will not be released to the subjects or to those individuals involved in managing or assessing safety in Part B of the study until that portion of the study is completed. Additional information can be found in the statistical analysis plan.

Date of Protocol: 05 June 2017

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DSPC	1,2 Distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
ELISPOT	enzyme-linked ImmunoSpot
EOS	end-of-study
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMR	geometric mean ratio
GMT	geometric mean titer
ICF	informed consent form
ICH	International Council for Harmonisation
IFNγ	interferon gamma
IM	intramuscular
IRB	institutional review board
IST	internal safety team
IV	intravenous
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MC3	DLin-MC3-DMA
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cell
PRNT50	Plaque Reduction Neutralizing TiterEC50
SAE	serious adverse event

Abbreviation	Definition
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
VLP	virus-like particle
WHO	World Health Organization
ZikaV	Zika virus

1 Introduction

1.1 Background

Zika virus (ZikaV) is a single-stranded RNA flavivirus, which is transmitted to humans by a mosquito vector (mainly *Aedes aegypti* but other *Aedes* mosquitoes are believed to be competent vectors) or by person-to-person spread, mainly through sexual transmission. ZikaV has been found in blood and other body fluids (saliva, urine, semen) in which it can persist longer than in the blood (Franca et al 2016). Due to the common vector, ZikaV has a similar epidemiology and transmission cycle to chikungunya and dengue. Most infections are either asymptomatic or result in a mild febrile illness with a rash. However, infection with ZikaV is also causally associated with Guillain-Barré syndrome neuropathy and other neurological sequelae in infected adults as well as congenital malformation of the brain (eg, microcephaly, ventricular calcifications) and other severe impairments (eg, intrauterine growth restriction) in infants born to mothers infected early in the pregnancy (Brasil et al 2016).

Currently there is no vaccine to protect against this disease, which has spread rapidly from Asia to most tropical and subtropical regions including the Americas. The Centers for Disease Control and Prevention (CDC) has listed ZikaV as a Level 1 alert (Brann 2016). The World Health Organization (WHO) has declared ZikaV to be a global public health emergency and has initiated a strategic framework to aid in rapid response (WHO, 2016a).

Moderna Therapeutics, Inc. has developed a proprietary messenger RNA (mRNA)-based vaccine platform. This is based on the principle and observations that antigens can be produced in vivo by delivery and uptake of the corresponding mRNA by cells. The mRNA then undergoes intracellular ribosomal translation to endogenously express the protein antigen(s) encoded by the vaccine mRNA. This mRNA-based vaccine does not enter the cellular nucleus or interact with the genome, is non-replicating, and expression is transient. mRNA vaccines thereby offer a mechanism to stimulate endogenous production of structurally intact protein antigens in a way that mimics wild type viral infection and is able to induce highly targeted immune responses against infectious pathogens such as ZikaV.

mRNA-1325 is an mRNA-based vaccine candidate being tested for its ability to safely induce an immune response with the intention to be able to prevent ZikaV infection.

1.2 Non-clinical Studies in Development of mRNA-1325

In support of development of mRNA-1325 for prophylaxis against ZikaV infection, a number of non-clinical efficacy, distribution, and safety studies are being completed. These studies are summarized in Table 1-1.

Table 1-1 Summary of Non-clinical Studies of mRNA-1325

Name of Study	Duration	Species	Route of Administration	Formulation
Efficacy				
An immunogenicity study to determine the ability of different doses of mRNA-1325 to induce IgG and neutralization titers (PRNT50) against homologous and heterologous strains of Zika	42 days	Mouse	IM	TRIS buffer pH 7.5
Safety				
A 6-week, repeat-dose safety and immunogenicity study of mRNA-1325 in Sprague Dawley® rat with 2-week recovery	6 weeks (3 doses 14 days apart) plus 2-week recovery	Sprague Dawley rat	IM and ID	TRIS buffer, pH 7.5
GLP 14-day tissue distribution study of VAL506440 mRNA in CD-1 mice	14 days	CD-1 mice	IM	TRIS buffer, pH 7.5
Ames bacterial reverse mutation assay with MC3 and PEG2000-DMG	Single exposure	*E coli* *S typhymurium*	In vitro	DMSO (PEG2000-DMG) Ethanol (MC3)
Mammalian cell micronucleus test in human PBLs with MC3 and PEG2000-DMG	Single exposure	Human cells	In vitro	DMSO (PEG2000-DMG) Ethanol (MC3)
An in vivo mouse micronucleus study of VAL-506440 containing MC3 and PEG2000-DMG LNPs	Single dose	Mouse	IV	20 mM citrate buffer, pH 6.7

Abbreviations: DMSO, dimethyl sulfoxide; GLP, Good Laboratory Practice; ID, intradermal; IgG, immunoglobulin G; IM, intramuscular; IV, intravenous; LNP, lipid nanoparticle; MC3, DLin-MC3-DMA; mRNA, messenger RNA; PBL, peripheral blood lymphocyte; PEG2000-DMG, 1,2-Dimyristoyl-sn-glycerol, methoxypolyethyleneglycol; PRNT50, Plaque Reduction Neutralizing Titer EC50.

1.2.1 Non-clinical Pharmacology

Based on clinical stage experiences with other flavivirus vaccines such as dengue (Dengvaxia™), the prME polyprotein is expected to be processed by cellular proteases and

form secreted, non-infectious virus-like particles (VLPs). Using a Western Blot, Moderna Therapeutics, Inc. has demonstrated that transfection of mRNA-1325 in human HEK293 cells results in the expression of the encoded prME antigen. Negative stain electron microscopy of the supernatant of these cultures reveals large numbers of VLPs that are uniform in size at the expected diameter of approximately 40 nM. Other nucleic acid-based vaccines have also recently demonstrated the ability of the prME to protect non-human primates from ZikaV (Larocca et al 2016).

1.2.2 Distribution

A branched DNA hybridization assay was developed for the quantification of mRNA in the plasma and tissues. This assay has been used successfully for detection of mRNA from another closely related influenza mRNA vaccine (VAL-506440 encoding the HA antigen from the H10N8 influenza strain). This assay provides excellent sensitivity (5-fg mRNA in 100-µg tissue) and specificity (200 to 400 base fragment of the mRNA with multiple probes) with a reasonable dynamic range (3-4 orders of magnitude).

A study describing lipid nanoparticle (LNP) distribution in tissues after extravascular (intradermal and intramuscular [IM]) administration indicated that the bulk of the dosed mRNA-1325 test article stayed near the site of administration (injection). It is highly improbable that a physiological mechanism exists that is capable of dramatic alteration of tissue distribution in closely related rodent species (rat vs mouse). With this consideration, Moderna Therapeutics, Inc. believes that the data obtained for mice are relevant to rats as well.

1.2.3 Toxicology

Given that the mRNA-1325 product consists of both an RNA component and an LNP component, Moderna Therapeutics, Inc. has proposed completion of a comprehensive toxicology study of all key components. An IND-enabling repeat-dose IM toxicology study has been completed in male and female rats to examine the safety of the full vaccine containing mRNA complexed with an LNP matrix. With regard to the safety of the novel excipient LNP components (DLin-MC3-DMA [MC3] and PEG2000-DMG), additional genetic toxicology studies consistent with International Council for Harmonisation (ICH) S2 R1 have been completed and include in vitro and in vivo genetic toxicology assessments. In support of development of mRNA-1325, the in vivo component of this assessment was performed with a fully formulated, identical LNP-mRNA drug product containing a different mRNA sequence,

VAL-506440. The full results of these repeat-dose toxicity and genetic toxicology studies are provided in the investigator's brochure.

1.2.4 Genotoxicity

mRNA-1325 is composed of not only mRNA, but also LNP components, cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), MC3, and PEG2000-DMG. Cholesterol and DSPC represent commonly used lipid excipients in numerous approved parenteral products. In contrast, MC3 and PEG2000-DMG represent novel lipids not contained in any products currently approved by the Food and Drug Administration (FDA). MC3 is a custom-manufactured, novel ionizable lipid that complexes with the active ingredient (mRNA) to form the LNP, while the 3 other commercial lipids (cholesterol, DSPC, and PEG2000-DMG) contribute to the overall pharmaceutical properties of the LNP. This type of lipid vehicle composition is currently in late-phase clinical studies conducted by Alnylam Pharmaceuticals to administer synthetic small interfering RNA via intravenous (IV) infusion in patients suffering from transthyretin amyloidosis, and was shown to be well-tolerated in this population (Coelho et al 2013). Over 2 years of human clinical experience in Phase 2 studies have been reported as of 2015.

In addition, both MC3 and PEG2000-DMG have also already been evaluated for safety and genotoxic potential in vitro and in vivo with the VAL-506440 H10N8 avian influenza vaccine. Given that these are the same lipid components in the mRNA-1325 drug product, Moderna Therapeutics, Inc. contends that additional new genetic toxicity studies with mRNA-1325 or the same component lipids MC3 and PEG2000-DMG would not be informative.

Moderna Therapeutics, Inc. has proposed completion of a Good Laboratory Practice (GLP) rat developmental and reproductive toxicology study, which will assess female Sprague Dawley rats only dosed at the highest anticipated clinical dose level and will include a control arm.

Further details on all non-clinical research on mRNA-1325 can be found in the investigator's brochure.

1.3 Clinical Studies with mRNA-1325

No clinical studies with mRNA-1325 have been conducted to date.

1.4 Rationale for Study

No vaccines have yet been licensed for prophylaxis of ZikaV infection. Of the approaches currently in development, the VLP and live attenuated vaccines (Akahata et al 2010; Darwin et al 2011; Wang et al 2008; Brandler et al 2013) show the greatest pre-clinical potential. However, both are expected to be more complex, costly, and longer to develop and scale-up than mRNA due to the need to establish, optimize, and characterize vaccine specific growth substrates, formulations, and dedicated production facilities. In addition, live attenuated vaccines, such as yellow fever vaccines, pose the risk of recombination with circulating wild type flaviviruses, reversion to pathogenicity, and vaccine-virus associated disease, particularly in immunocompromised populations. The Sponsor believes that on the basis of pre-clinical data with this and other vaccines in the Moderna Therapeutics, Inc. development pipeline, mRNA-1325 has the potential to achieve at least equivalent and more predictable levels of efficacy and safety, with more rapid and reliably scalable manufacturing.

The purpose of this Phase 1, first-in-human, randomized, placebo-controlled, dose-ranging, study is to evaluate the safety and immunogenicity of mRNA-1325 in healthy adult subjects in a non-endemic region. The primary objective of this study is to assess the safety profile of mRNA-1325 compared with placebo. The study will also evaluate immunogenicity by assessing changes from Baseline in ZikaV-specific neutralizing antibody titers. The safety profile and immune response(s) will be compared between flavivirus-seropositive and flavivirus-seronegative subjects to indicate the ability of the selected dose to safely protect populations in both endemic and non-endemic regions.

1.5 Rationale for Dose Selection

Dosing will begin with 10 µg (Cohort 2), followed by 25 µg (Cohort 3), and then 100 µg (Cohort 4). There will be no Cohort 1 included in this study. The 10 µg dose was chosen as a starting dose based on both pre-clinical data with mRNA-1325 and clinical data from two Phase 1 trials with different mRNAs in the same formulation as mRNA-1325. The pre-clinical no-observed-adverse-effect level (NOAEL) was established as 50 µg for repeated IM dosing in the rat. This supports the starting dose of 10 µg in this study.

In an ongoing clinical study with the Moderna mRNA H10N8 influenza vaccine, which utilizes the same the lipid composition as mRNA-1325, the tolerability profile of the vaccine administered according to a 2-dose vaccination schedule in a dose range of 25 µg to 100 µg

was acceptable, and the vaccine induced a robust immune response. According to Bahl and colleagues (Bahl et al 2017), the majority of solicited AEs reported in the 100-µg group were mild (107/163 events; 66%) or moderate (52/163 events; 32%). The majority of events were injection site pain, myalgia, headache, fatigue, and chills/common-cold-like symptoms. Only 4 events (2.5%), reported by 3 subjects, were categorized as severe and included injection site erythema (1.2%), injection site induration (0.6%), and chills/common cold (0.6%). No related SAEs occurred in the study.

In order to inform dose choices in this study, Moderna performed a group unblinding analysis of immunogenicity data from the first dose cohort (ie, Cohort 2: 10 µg of mRNA-1325). The analysis confirmed that the vaccine is able to induce neutralizing antibodies against Zika virus in both flavivirus-seronegative and flavivirus-seropositive subjects. Following review of the immunogenicity results from this cohort and considering the variability of the serological assay and the biological variability of the immune response, Moderna decided to increase the dose for Cohort 4 from 50 µg to 100 µg.

Available non-clinical and clinical data support the starting dose in this study of 10 µg and a maximum dose of 100 µg.

1.6 Rationale for Study Design

The study is designed to generate the safety and immunogenicity data required to select the optimal dose of mRNA-1325 for further development in both endemic and non-endemic populations. Pre-clinical and clinical data support the expectation that a 2-dose vaccination schedule, 1 month apart, will induce a protective immune response. This 2-dose schedule will be explored at a range of doses in 2 subpopulations: Non-endemic populations are represented by subjects recruited from the general population who are expected to be largely flavivirus seronegative. This is confirmed through a baseline West Nile serology screening test, which if negative, excludes the most prevalent flavivirus infection in the United States. Cross-reactivity of this test with other flaviviruses will establish a high certainty of baseline flavivirus naïvety in this population. In addition, a proportion of subjects will be recruited who have received a flavivirus vaccination (yellow fever) within the preceding 20 years in order to assess the safety and immunogenicity profile in a homogeneous flavivirus-seropositive population in order to represent an endemic population.

In order to explore vaccine tolerability, dosing will begin with 10 µg (Cohort 2), and escalation to 25 µg and 100 µg will require review by the SMC of safety data collected from the preceding dose level cohorts. A dose-level cohort at 10 µg will be included to complete the dose ranging for safety and immunogenicity. For each cohort, a sentinel safety group will enroll 3 flavivirus-seronegative subjects randomized to mRNA-1325 and followed for 7 days after first vaccination, with review of reactogenicity (Section 3.5.6) and safety laboratory results, prior to randomizing the remainder of the cohort. In addition, pause rules have been pre-established to trigger ad hoc SMC reviews, if required, and an internal safety team (IST) will review (blinded review) clinically significant safety laboratory test results, vital sign measurements, reactogenicity, and any AEs (all with toxicity scoring/grading) during the active vaccination phase of the trial.

Immunogenicity will be assessed on the day of vaccination (before vaccination) and 7 (+3) (cellular) and 28 (+7) (humoral) days following each vaccination. Longer-term safety and immune persistence will be monitored for at least 1 year in a blinded follow-up period (Part B). Immune persistence at 168 days and 364 days will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence. Data will be encoded into a safety database that will capture long-term safety across multiple Phase 1 (and possibly Phase 2) studies for this proprietary mRNA vaccine technology to allow safety to be monitored at the mRNA platform level.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to assess the safety of a 2-dose vaccination schedule of mRNA-1325 Zika vaccine, given 28 days apart, across a range of dose levels in flavivirus-seronegative and flavivirus-seropositive subjects compared with placebo.

2.2 Secondary Objective

The secondary objective of this study is to assess the immunogenicity of a range of doses of mRNA-1325 Zika vaccine and to select a dose for further development, based on changes from Baseline in the following tests:

- ZikaV-specific neutralizing antibody titers measured by a Plaque Reduction Neutralizing Titer EC50 (PRNT50);

2.3 Exploratory Objective

The exploratory objectives of this study are to:

- Assess the impact of mRNA-1325 Zika vaccine on a range of other functional and diagnostic flavivirus assays.
    - Assess ZikaV antigen-specific stimulation of T cells measured by interferon gamma (IFNγ) enzyme-linked ImmunoSpot (ELISPOT) on subject-derived peripheral blood mononuclear cells (PBMCs), if results of interim immunogenicity analyses warrant further analyses of samples .

3 Investigational Plan

3.1 Study Design

This is a Phase 1, double-blind, placebo-controlled, dose-finding study to evaluate the safety and immunogenicity of a range of dose levels of mRNA-1325 Zika vaccine given in a 2-dose vaccination schedule, 28 days apart, and compared with placebo in healthy adult subjects (18 to 49 years of age, inclusive). mRNA-1325 is an mRNA-based vaccine candidate being tested for its ability to safely induce an immune response able to prevent ZikaV infection.

ZikaV is a single-stranded RNA flavivirus, which is transmitted to humans by a mosquito vector (mainly *Aedes aegypti* but other *Aedes* mosquitoes are believed to be competent vectors) or by person-to-person spread, mainly through sexual transmission. Currently there is no vaccine to protect against this disease, which has spread rapidly from Asia to most tropical and subtropical regions including the Americas.

This is a 2-part study. Part A includes dose-finding, safety, and immune testing through 28 days following the second vaccination. Once subjects complete the final visit in Part A, they will be entered into Part B. Part B is a blinded follow-up period with assessment of safety through 12 months and immune persistence at 168 (±15) days and 364 (+15) days following the second vaccination in Part A. Immune persistence at 168 days and 364 days will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence.

Part A

Subjects will be randomly assigned in a blinded fashion in an approximate 4:1 ratio to receive mRNA-1325 or placebo at 1 of 3 dose levels (10 µg, 25 µg, or 100 µg), with each subject receiving 2 vaccinations separated by 28 (+7) days. Dosing will begin with 10 µg (Cohort 2), followed by 25 µg (Cohort 3), and then 100 µg (Cohort 4). There will be no Cohort 1 included in this study. Approximately two-thirds of the enrolled subjects at each dose level will be flavivirus naïve and approximately one-third will be flavivirus seropositive as a result of having received a yellow fever vaccination in the past 20 years by either: a) military assignment in the previous 20 years that requires a yellow fever vaccination; or 2) yellow fever vaccination documented on an international certificate or other confirmatory documentation of yellow fever vaccination.

Cohort and treatment assignment are shown in Figure 3-1.

Figure 3-1 Cohort and Treatment Assignment

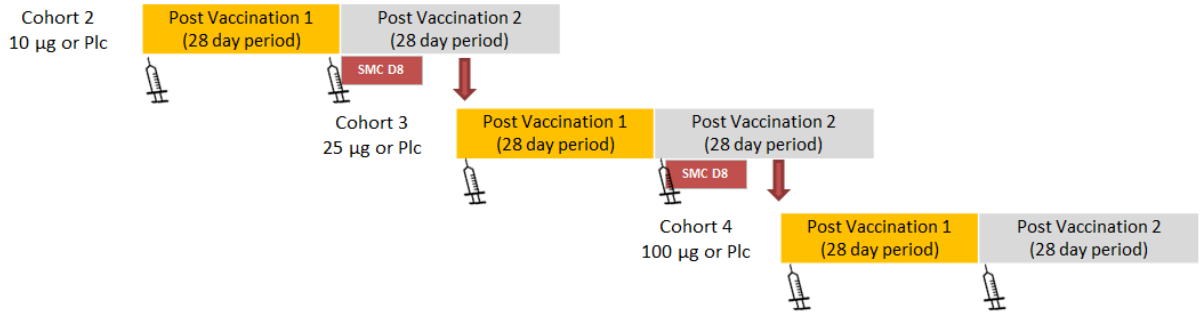
Cohort	Flavivirus Status	Treatment Assignment (µg mRNA-1325 or placebo)	Total (Ratio)
2	+	10	30 (4:1)
	-	10	
	+	placebo	
	-	placebo	
3	+	25	30 (4:1)
	-	25	
	+	placebo	
	-	placebo	
4	+	100	30 (4:1)
	-	100	
	+	placebo	
	-	placebo	

Abbreviations: +, flavivirus seropositive; -, flavivirus seronegative.

For each cohort, a sentinel safety group will occur with 3 flavivirus-seronegative subjects randomized to mRNA-1325 and followed for 7 days after first vaccination, with review of reactogenicity and safety laboratory results, prior to randomizing the remainder of the cohort. An IST will oversee the safety of the trial and will review blinded safety data during Part A of the study to ensure adherence to the protocol, monitor safety laboratory test results and reactogenicity, and raise concerns to the SMC should there be safety issues or operational challenges that could affect subject safety. Only after review by the IST of the blinded safety data (reactogenicity, safety labs, and AEs) through 7 days following first vaccination of the sentinel safety lead-in for each cohort planned will approval be given to allow randomization of the remainder of that cohort. The SMC will approve escalation to the next higher dosing cohort after review of blinded safety data of the currently dosed cohort through 7 days following the second vaccination and any cumulative safety data of all cohorts as the trial advances. The SMC will also be convened (ad hoc meeting) if a pause rule is triggered.

A diagram of the dosing schema by cohort is shown in Figure 3-2.

Figure 3-2 Dosing Schema by Cohort



Abbreviations: D, day; Plc, placebo; SMC, safety monitoring committee.

Note: Yellow shading depicts safety follow-up of the first vaccination period and grey shading depicts safety follow-up of the second vaccination period for cohorts by dose sequence.

Note: The SMC will approve escalation to the next higher dosing cohort after review of blinded safety data of the currently dosed cohort through 7 days following the second vaccination and any cumulative safety data of all cohorts as the trial advances.

The vaccine will be administered as an IM injection (0.5 mL) into the deltoid muscle as a 2-dose vaccination schedule at Visits 1 and 4 (at least a 28-day interval between dosing). The second dose of study drug will be administered preferably in the same arm used for the first dose. Vaccine accountability, dose preparation, and vaccine administration will be performed by unblinded pharmacy personnel, who will not participate in any other aspect of the study. The remainder of the site staff and all subjects will remain blinded to treatment assignment.

Screening and consent will occur over a 28-day period before randomization (West Nile virus serology screen can occur up to 90 days prior to randomization). A total of 30 subjects for each dose cohort will be assigned, 24 subjects to mRNA-1325 and 6 subjects to placebo (approximate 4:1 ratio overall). The first 3 subjects for each dose level will be randomized to mRNA-1325. Subjects who meet all eligibility criteria will receive the first vaccination at Visit 1. Of note, a subject who has met all eligibility criteria but is noted to have a blood pressure, heart rate or respiratory rate that is Grade 2 or greater (even after relaxing/resting) in the clinic on the day of vaccination should not receive a vaccination on that day and will need to return on a subsequent day for their vaccination. Similarly, if a subject has a fever (>37.9°C) or an intercurrent illness, vaccination should be withheld until resolved (as specified in exclusion criterion 20). Each subject will be monitored in the clinic for at least 1 hour following vaccination to assess for immediate reactogenicity, with vital sign measurements and local and

systemic reactogenicity toxicity scored at that time. The highest toxicity recording will be entered into the electronic case report form (eCRF).

Subjects will be instructed on recording reactogenicity, AEs, and medications (prescription or over-the-counter) on the memory aid (ie, diary card), and will be provided measuring tools, and instructed to call or return to the clinic within 24 hours if a reactogenicity score reaches Grade 3 or greater during the first 7 days following vaccination. As standard practice, a reminder call will be made to the subject by the site at least once during the first 7 days following each vaccination to answer any questions and ensure that the memory aid is being completed correctly and consistently. All subjects will return on 7 (+3) (cellular PBMC testing) and 28 (+7) (humoral neutralization testing) days following each vaccination for safety assessments and blood sampling for immune testing.

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity) events (first 7 days after each vaccination); clinical laboratory test results including hematology, serum chemistry, coagulation, and urinalysis; vital sign measurements; and physical examination findings (Day 7 after each vaccination) and unsolicited AEs (throughout Part A). All unsolicited AEs and concomitant medication (including over the counter) usage will be collected. Specific categories of safety data collected will include SAEs, AEs of special interest (AESIs), AEs leading to study withdrawal, and medically attended AEs. At clinic visits, the investigator will review, confirm, and grade the reactogenicity recorded in the memory aid and inquire about and review AEs and medications.

All safety laboratory tests will be performed according to Table 6-1. Safety laboratory tests will be performed during Screening (to allow for assessment of inclusion and exclusion criteria), on the day of first vaccination (Visit 1), 7 (+3) days following each vaccination (Visit 2 and Visit 5), and 28 (+7) days following each vaccination (Visit 4 [prior to second vaccination] and Visit 7). At 17 (±3) days following each vaccination (Visit 3 and Visit 6) and at 21 [+3] days after the first vaccination (Visit 3a) for the sentinel subjects, a subset of safety laboratory tests will be performed as specified in Table 6-1. Blood test results (pre-vaccination) at Visit 1 will be the basis for evaluation of changes from Baseline after vaccination.

Blood samples for immunogenicity assessments (cellular and humoral) will be collected the day of vaccination (before vaccination) and 7 (+3) and 28 (+7) days, respectively, following each vaccination. Subjects that miss the second vaccination due to noncompliance with the visit schedule and not due to a cohort pause will still be required to follow the original visit

and testing schedule. These subjects will be asked to undergo blood collection to comply with a second immune test at Visit 7 (56+7 days after first vaccination).

To allow cohort advancement, the following data from the highest dosed cohort is expected to be reviewed by the SMC: 1) toxicity scoring of safety laboratory test results through 7 days following the second vaccination (through Visit 5); 2) toxicity scoring of vital signs and reactogenicity through 7 days following the first and second vaccination (through Visit 5); 3) all unsolicited AEs (with grading and relatedness). Data will be prepared by dose category and timing relative to the last vaccination. As safety data on all cohorts accumulate, the SMC also review ongoing AEs as well as cumulative safety laboratory test results, reactogenicity, and AEs across vaccine doses for subjects remaining in Part A of the study, thereby providing a cumulative and comprehensive review of safety. Should a cohort pause occur due to pre-specified criteria, the SMC will be convened for an unscheduled (ad hoc) meeting and be provided with specific safety data related to the trigger of the pause.

Part A is concluded for each subject at the time when they return to the clinic for Visit 7 (28 days following the second vaccination). At that time, a subject will be entered into Part B of the study. Once query resolution and immune testing is completed for each cohort in Part A, the database will be locked. Results will be provided to the Sponsor, SMC, and IST. The Sponsor may determine whether dosing adjustments are required during the conduct of the study based on either safety or immune responses per cohort. As dose escalation occurs, cumulative analyses will be included for each subsequent data lock to allow for all prior dosing cohorts to be analyzed by cohort, treatment assignment, and in aggregate for mRNA-1325 exposure. Subject-level individual treatment assignment will not be released to the subjects or to those individuals involved in managing or assessing safety in Part B of the study until that portion of the study is completed.

The full schedule of events for Part A is shown in Table 6-1.

Part B – 12 Month Follow-up After Final Vaccination

To monitor for longer-term safety and immune persistence, each subject will be entered into a continued, blinded follow-up period (Part B). This period will be conducted such that subjects, observers, and safety monitors will remain blinded to treatment assignment. Part B of the study is initiated for a subject once they have returned for Visit 7 (28 days following the second vaccination). The safety database utilized for Part B may be accessed by the pharmacovigilance

safety team for safety signal detection at scheduled intervals for ongoing assessments for a given vaccine candidate as well as for the mRNA platform technology.

Once entered into Part B, each safety contact will occur by telemedicine (eg, telephone, text message, internet) every 28 (±7) days, and blood samples for immune persistence will be collected from each subject at 168 (±15) days and 364 (+15) days following the second vaccination. Immune persistence at 168 days and 364 days will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence. Each safety contact will capture outcomes of any AESI or SAE that remains unresolved since the last visit or is newly identified through scripted query. The telemedicine visits may require additional data through medically attended visits, in addition to and medications and vaccination taken by the subject during this time. Subjects will have consented during study enrollment to allow access to additional medical records needed to complete Part B, thereby allowing the blinding of the treatment assignment to be maintained.
The full schedule of events for Part B is shown in Table 6-2.

When all subjects have completed their final contact (approximately 12 months after their last vaccination), immune testing is completed, and all queries resolved, the database will be locked and analyzed with a final clinical study report provided to regulators.

3.2 Selection of Study Population

Healthy male or female subjects will be enrolled in at least 2 sites in the United States or its territories. Approximately 90 subjects are planned to be randomly assigned to receive study treatment.

3.2.1 Inclusion Criteria

Each subject must meet all of the following criteria during the screening period to be enrolled in this study:

1. The subject is male or female between 18 and 49 years of age, inclusive.

2. The subject has a body mass index between 18 and 35 kg/m^2, inclusive.

3. The subject is considered by the investigator to be in good general health as determined by medical history.

4. Female subjects must be non-pregnant and non-lactating and meet one of the following criteria: a) post-menopausal (defined as 12 consecutive months with no menses without an

alternative medical cause or documented plasma follicle-stimulating hormone level in the post-menopausal range); b) surgically sterile (ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). NOTE: these procedures and laboratory test results must be confirmed by physical examination or official written confirmation of a procedure; c) if of childbearing potential (defined as any female who has experienced menarche and who is NOT permanently sterile or post-menopausal), agrees to be heterosexually inactive from at least 21 days prior to enrollment and through 3 months after the final vaccination or agrees to consistently use any of the following methods of contraception from at least 21 days prior to enrollment and through 3 months after the final vaccination: condoms (male or female) with spermicide, diaphragm with spermicide, cervical cap with spermicide, intrauterine device, oral or patch contraceptives, Norplant®, Depo-Provera®, or other FDA-approved contraceptive method that is designed to protect against pregnancy. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects must use an acceptable method of birth control (see above) and must also agree to refrain from donation of sperm from the time of first vaccination until 3 months following the last vaccination. Periodic abstinence, declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.

5. Subject assigned to the flavivirus-seropositive group has received a yellow fever vaccination in the past 20 years by either: a) military assignment in the previous 20 years that requires a yellow fever vaccination; or 2) yellow fever vaccination documented on an international certificate or other confirmatory documentation.

6. The subject understands and agrees to comply with the study procedures and provides written informed consent.

7. The subject has access to a consistent and reliable means of telephone contact, which may be in the home, workplace, or by personal mobile electronic device.

8. The subject agrees to stay in contact with the study site for the duration of the study, to provide updated contact information as necessary, and has no current plans to move from the study area for the duration of the study.

3.2.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has any ongoing significant chronic illness requiring medical or surgical care. Asymptomatic conditions or findings (eg, mild hypertension, dyslipidemia) that are not associated with evidence of end-organ damage are not exclusionary provided that they are being appropriately managed and are clinically stable in the opinion of the investigator (ie, unlikely to result in symptomatic illness within the time-course of this study).

2. The subject has a history of active cancer (malignancy) in the last 10 years (exception is subjects with adequately treated non-melanomatous skin carcinoma, who may participate in the study).

3. The subject is a female of childbearing potential and has a positive pregnancy test at Screening or on the day of vaccination.

4. The subject has abnormal liver enzyme tests (increase in aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase) at Screening.

5. The subject has received another investigational product in another investigational study within 60 days, or 5 half-lives, whichever is longer, before the planned date of first vaccination.

6. The subject has received any live attenuated vaccines within 4 weeks before enrollment or inactive vaccines within 2 weeks before enrollment, or plans to receive any vaccine during the active vaccination period (through 4 weeks after their last planned vaccination).

7. The subject has received (at any time) a vaccine for Zika or dengue vaccine.

8. The subject has a history of confirmed Zika or dengue infection.

9. The subject has lived in or visited any Zika-endemic area (as defined by WHO; Appendix 4) greater than 4 weeks in duration (flavivirus-seronegative group, only).

10. The subject has received any vaccination for a flavivirus (eg, yellow fever, Japanese encephalitis) in his or her lifetime (flavivirus-seronegative group, only), or received a vaccination for a flavivirus more than 20 years ago (flavivirus-seropositive group, only).

11. The subject has a positive West Nile virus antibody titer above the detection level of the assay (flavivirus-seronegative group, only). NOTE: West Nile virus titers are considered valid for a period of 90 days (allowing for the screening period on West Nile virus to exceed the standard 28 days as noted for all other screening parameters).

12. The subject has reported previously participating in an investigational study involving LNPs.

13. The subject has a history of hypersensitivity or serious reactions (eg, anaphylaxis, urticaria, other significant reaction) to previous vaccinations.

14. The subject has any known or suspected autoimmune disease or immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination.

15. The subject has a history of inflammatory arthritis.

16. The subject has a neurologic disorder (eg, history of seizures, Guillain-Barré syndrome, dementia, vasculitis, or any known congenital or acquired disorder).

17. The subject has a history of febrile disease with arthritis or arthralgia within 2 weeks of dose administration.

18. The subject received immunoglobulins and/or any blood products within the 3 months preceding the administration of the study drug or plans to receive such products at any time during the study.

19. The subject has had chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune-modifying drug within 6 months before vaccine administration or plans to receive any products during the active vaccination period (through 4 weeks after their last planned vaccination). An immunosuppressant dose of a glucocorticoid will be defined as a systemic dose of ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

20. The subject has any acute illness at the time of enrollment (defined as the presence of a moderate or severe illness with or without fever, or an oral body temperature >37.9°C on the planned day of vaccination). In such cases, subjects may be re-evaluated during the

screening period for resolution of the illness to allow at least 3 days of wellness before the planned vaccination as long as they remain within the 28-day screening period.

21. The subject has any significant disorder of coagulation (acquired or hereditary) requiring ongoing or intermittent treatment. Subjects receiving prophylactic antiplatelet medications, eg, low dose acetylsalicylic acid (≤100 mg/day or equivalent), and without clinically apparent bleeding tendency, are eligible.

22. The subject has a history of idiopathic urticaria.

23. The subject has a documented history of alcohol abuse or drug addiction within 1 year before the planned day of dose administration.

24. The subject has a positive test result for drugs of abuse at Screening or on the day of first vaccination.

25. The subject has any abnormality or permanent body art (eg, tattoo) that, in the opinion of the investigator, would obstruct the ability to observe local reactions at the injection site (deltoid region).

26. The subject has any condition that, in the opinion of the investigator, would pose a health risk to the subject if enrolled or could interfere with evaluation of the study drug or interpretation of study results (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).

27. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies.

28. The subject has donated blood or blood products >450 mL within 30 days of dosing.

29. The subject has screening safety laboratory test results (urine and serum) outside the normal range of the laboratory and with a toxicity score with Grade 1 or higher.

30. The subject has screening vital sign of blood pressure, heart rate, or respiratory rate that is equal to or greater than Grade 1 by toxicity score.

31. The subject is an employee or first degree relative of the Sponsor, PPD, or study site personnel.

Note that some exclusion criteria are time-related. A subject may be re-evaluated on more than one occasion during the screening period to assess for resolution. There is allowance to repeat an abnormal vital sign measurement and Grade 1 laboratory abnormalities (except aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) once to allow for inclusion into the study and the last value measured will be used to allow inclusion in the study.

3.2.3 Subject Restrictions During the Study

3.2.3.1 General and Dietary

To avoid false positive drugs of abuse Screening results, subjects should refrain from food or drink containing poppy seeds (eg, specialty breads and muffins) for 72 hours before the screening visit.

3.2.3.2 Contraception and Pregnancy Avoidance Procedures

Female subjects **not** of childbearing potential must (defined as any female who has experienced menarche and who is NOT permanently sterile or post-menopausal) be post-menopausal (defined as amenorrhea for 12 consecutive months without an alternative medical cause or documented plasma follicle-stimulating hormone level in the post-menopausal range) or surgically sterile (ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). NOTE: these procedures and/or laboratory test results must be confirmed by physical examination or be provided through medical documentation. If of childbearing potential, female subjects must be practicing a medically approved and highly effective method of contraception (defined as those which result in a low failure rate [ie, less than 1% per year] when used consistently and correctly).

All female subjects of childbearing potential must have a negative pregnancy test at Screening and before dosing with study drug. Women of childbearing potential must agree to be heterosexually inactive from at least 21 days prior to enrollment and through 3 months after the final vaccination or agree to consistently use any of the following methods of contraception from at least 21 days prior to enrollment and through 3 months after the final vaccination: condoms (male or female) with spermicide, diaphragm with spermicide, cervical cap with spermicide, intrauterine device, oral or patch contraceptives, Norplant®, Depo-Provera®, or other FDA-approved contraceptive method that is designed to protect against pregnancy. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male subjects must use an acceptable method of birth control throughout the entire study (see above). Males must also agree to refrain from donation of sperm from the time of first vaccination until 3 months following the last vaccination. Periodic abstinence, declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.

Female subjects of childbearing potential and male subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy.

3.3 Withdrawal of Subjects From the Study

3.3.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator can also withdraw a subject, upon the request of Moderna Therapeutics, Inc. or if Moderna Therapeutics, Inc. terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the Sponsor or designee. If a subject desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to continue to follow that subject for that event only until it is resolved or until stable and then complete an EOS form. In the event of a safety concern that results in withholding from further vaccination, the subject will be continued in the trial for safety evaluations.

Every reasonable attempt will be made to follow subjects for safety throughout the entire trial period even if further vaccination is withheld or the subject misses visits. The reason for subject withdrawal or lost to follow-up will be documented.

The investigator, in consultation with the Sponsor's medical monitor, **may** withhold a subject **from further vaccination** if the subject experiences any of the following:

1. Becomes pregnant;

2. Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria;

3. Experiences an AE (other than reactogenicity) after vaccination that is considered by the investigator to be possibly or probably related to treatment and is of Grade 3 (severe) or higher severity;

4. Experiences an AE or SAE that, in the judgment of the investigator, requires study drug withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to treatment;

5. Experiences a clinically significant change in clinical laboratory test results, vital signs, or general condition that, in the judgment of the investigator, requires treatment withdrawal;

6. Experiences anaphylaxis clearly attributed to study vaccine;

7. Experiences generalized urticaria related to the study vaccine.

The reason for withdrawing or refusing from further vaccination will be recorded. In addition, if a subject refused further vaccination they will be continued in the trial with all planned visits and assessments relative to the vaccination schedule and including visits through 1 year post final vaccination.

3.3.2 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the eCRF. These subjects will also be requested to complete all Visit 7 assessments. Any subject who fails to return for final assessments will be contacted by the site with a minimum of 3 phone call attempts, followed by a certified letter. After this final attempt the subject will be declared “lost to follow-up” on the EOS.

Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, text messages, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject’s source documents.

3.3.3 Replacements

Any subject who is withdrawn, who is significantly outside the allowed vaccination window, or is lost to follow-up from the study will not be replaced without the prior authorization of the Sponsor.

3.4 Study Treatments

3.4.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to a cohort after all entry criteria have been satisfied on Visit 1. A randomization table will be pre-generated, and only the unblinded pharmacy personnel will have controlled access. Subjects will be randomly assigned in a blinded fashion in an approximate 4:1 ratio to mRNA-1325 or placebo at 1 of 3 dose levels (10 µg, 25 µg, or 100 µg). The first 3 subjects for each dose level will be randomized to mRNA-1325. Approximately two-thirds of the enrolled subjects at each dose level will be flavivirus naïve and approximately one-third will be flavivirus seropositive as a result of having received a yellow fever vaccination in the past 20 years.

3.4.2 Treatments Administered

Dosing will begin with 10-µg mRNA-1325 or placebo (Cohort 2), followed by 25-µg mRNA-1325 or placebo (Cohort 3), and then 100-µg mRNA-1325 or placebo (Cohort 4). The rationale for dose selection is described in Section 1.5. Dosing cohorts will advance as described in Section 3.4.2.1.

Vaccine will be administered as an IM injection (0.5 mL) into the deltoid muscle as a 2-dose vaccination schedule at Visits 1 and 4 (at least a 28-day interval between dosing). The second dose of study drug will be administered preferably in the same arm used for the first dose.

The clinic will be appropriately staffed, trained on emergency resuscitation, and have stocked available rescue medications (such as epinephrine, steroids, antihistamines, and IV fluids) should any severe reaction (eg, anaphylaxis or profound urticaria) occur that requires immediate intervention.

3.4.2.1 Dose Escalation

Internal Safety Team

An IST will oversee the safety of the trial and will review blinded safety data during Part A of the study to ensure adherence to the protocol, monitor safety laboratory test results and reactogenicity, and raise concerns to the SMC should there be safety issues or operational challenges that could affect subject safety. Pause rules have been pre-established to trigger ad hoc SMC reviews, if required (Section 3.4.2.2), and the IST will review (blinded review) safety

laboratory test results, vital sign measurements, reactogenicity, and any AEs (all with toxicity scoring/grading) during the active vaccination phase of the trial. In addition, recruitment rates, timing of vaccination sequence, and window adherence will be reported to the IST. The chairperson of the IST may request that additional data be provided to the SMC that relates to the safety of subjects (eg, study conduct, quality issues, or safety concerns).

At minimum, the IST will be composed of the Sponsor's study medical monitor lead, the contract research organization's medical monitor, and the principal investigator(s). The medical monitor will oversee safety aspects of the study and will participate as needed. Additional ad hoc members may be included as needed.

Safety Monitoring Committee

The SMC will review data for dose escalation when at least 90% of subjects dosed (eg, ≥27 out of 30 subjects) in Cohort 2 (10-µg mRNA-1325 or placebo) have safety data inclusive of their visit 7 days following the second vaccination (Visit 5). Once a recommendation is given by the SMC, the Sponsor will approve advancing to Cohort 3 (25-µg mRNA-1325 or placebo). Cohort 4 (100-µg mRNA-1325 or placebo) will be randomized following SMC review and Sponsor approval of Cohort 3 (data inclusive of 7 days following the second vaccination of ≥90% of subjects dosed [eg, ≥27 out of 30 subjects]).

To allow cohort advancement, the following data from the highest dosed cohort is expected to be reviewed by the SMC: 1) toxicity scoring of safety laboratory test results through 7 days following the second vaccination (through Visit 5); 2) toxicity scoring of vital sign measurements and reactogenicity through 7 days following the first and second vaccination (through Visit 5); 3) all unsolicited AEs (with grading and relatedness). Data will be prepared by dose category and timing relative to last vaccination. As safety data on all cohorts accumulate, the SMC will include in their review ongoing AEs as well as cumulative safety laboratory test results, reactogenicity, and AEs across vaccine doses as long as subjects remain in Part A of the study, thereby providing a cumulative review of safety. Should a cohort pause occur due to pre-specified criteria (Section 3.4.2.2), the SMC will be convened for an unscheduled (ad hoc) meeting and receive specific safety data related to the trigger of the pause.

The SMC may recommend advancement to the next dosing cohort, request additional information prior to providing a recommendation, recommend stopping the study, recommend changes to study conduct and/or the protocol, or recommend additional operational

considerations due to safety issues that arise during study conduct. The Sponsor has the authority to accept (or amend) the SMC recommendations, to stop the study at any time, to request a cohort pause for safety concerns (to be addressed by the SMC), and to request additional consultation during study conduct for either safety concerns or operational issues. The SMC will also be convened should a pause rule be triggered or at the request of the IST, the investigator(s), or the Sponsor.

The SMC will be comprised of 3 voting and independent members who are medical doctors familiar with Phase 1 clinical trial and safety review and independent from the trial. In addition, a biostatistician not associated with the trial will prepare the safety data (non-voting member), and a coordinator not associated with the trial will organize and record decisions of the SMC (non-voting member). The SMC may decide to include a non-medical person to weigh in on ethical issues if the need arises.

3.4.2.2 Pause Rules

During the active vaccination period, if any of the following events occur and are assessed to be potentially mRNA-1325 related, the cohort will be paused for further enrollment and vaccination, and an unscheduled SMC will be convened to assess specific data concerns and make recommendations:

- Two or more Grade 3 (or greater) reactogenicity events (whether systemic or local) within a dose cohort following any single (eg, the first, the second) vaccination
- Two or more Grade 3 (or greater) same laboratory toxicity score within a dose cohort
- One or more SAEs assessed as vaccine related, including any systemic hypersensitivity reaction

An unscheduled SMC may also be convened (with vaccination pausing if deemed necessary), by the investigator, IST, or Sponsor, if any other significant safety or tolerability issues are identified in the comprehensive review of available data that warrant further evaluation before additional subjects are dosed. This may include emerging non-clinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns even if the event(s) per se does not meet the criteria specified in this section.

Should a pause be triggered in the study, then each subject's visits will continue until the next scheduled vaccination visit. Should a pause affect a subject's vaccination visit, then the window for that subject's vaccination visit will be suspended until the pause is lifted and vaccination can resume. Once the pause is lifted at the site, vaccination should be reinstated as soon as possible. Visits should thereafter be scheduled as if they had received their second vaccination within the 28 (+7) day time window.

Should a pause be prolonged such that the second vaccination takes place outside the 28 (+7) day time window, the Sponsor has the option to add additional subjects in a dosing cohort to achieve the original number of subjects planned to be dosed within the 28 (+7) day time window. If a subject is in the screening period for more than 28 days as the result of a pause, they may be rescreened for study eligibility as long as they continue to provide consent to participate in the study.

Dosing adjustments may be made during the conduct of the study should the data reveal the need to adjust dosing due to the observed immune response or a change in the perceived benefit:risk ratio. However, treatment assignment will not be released to the subjects or to those individuals involved in managing or assessing safety in Part B of the study until Part B of the study is completed.

3.4.3 Identity of Investigational Product

The mRNA-1325 Injection consists of the mRNA drug substance, mRNA-1325, which encodes the ZikaV prME polypeptide, in an LNP formulation intended for IM injection. The mRNA-1325 LNP formulation includes 4 lipid excipients: MC3, an ionizable amino lipid (Jayaraman et al 2012), and the commercially available lipids cholesterol, DSPC, and PEG2000DMG (Mui et al 2013), at a molar ratio of 50:38.5:10:1.5 for MC3:cholesterol:DSPC:PEG2000-DMG. At pH below 6, the MC3 lipid is positively charged and binds to the negatively charged mRNA, thereby facilitating the formation of the mRNA/lipid complexes. Cholesterol is incorporated to provide structure and physicochemical stability to the particles. The neutral "helper" lipid, DSPC, is incorporated in order to increase the fusogenic properties of the particles. The polyethylene glycol lipid conjugate PEG2000-DMG confers surface stabilization to the nanoparticles. The drug product formulation comprises 1.3 mg/mL mRNA-1325 drug substance and 26 mg/mL total lipid concentration.

The placebo is 0.9% Sodium Chloride Injection, USP or BP.

3.4.4 Management of Clinical Supplies

3.4.4.1 Study Drug Packaging and Storage

Moderna Therapeutics, Inc. will provide the investigator and study site with adequate quantities of mRNA-1325 Injection. The placebo (0.9% Sodium Chloride Injection, USP or BP) is commercially available and will be supplied by the Sponsor or PPD. mRNA-1325 Injection will be labeled "for clinical trial use" and have all required labeling per regulations. mRNA-1325 Injection will be supplied to the pharmacy in an unblinded manner. Each vial will be individually labeled for future subject identification purposes.

mRNA-1325 Injection will be supplied in 2-mL glass vials with a 0.5-mL fill volume. The unblinded study site pharmacy personnel will prepare a single dose (0.5 mL) for each subject based on the cohort and randomization assignment. A single vial may be used for multiple subjects in a given day as long as the storage conditions are met and the vaccine is not refrozen. A pharmacy manual will be available and training provided to ensure pharmacy staff can comply with all vaccine storage, preparation, administration, and drug accountability procedures.

mRNA-1325 Injection must be stored in a secure area with limited access (unblinded pharmacy staff only), protected from moisture and light, and be stored at −20°C ± 5°C. The freezer should have an automated temperature recording and alert system. There must be an available back-up freezer. The freezers must be connected to a back-up generator. The pharmacy must have in place a 24-hour alert system that allows for rapid response in case of freezer malfunctioning. In addition, drug accountability study personnel (eg, the unblinded pharmacy staff) are required to keep a temperature log to establish a record of compliance with these storage conditions. The placebo will be stored according to the instructions on the product label and must also comply with storage in a restricted access area. Only drug accountability (eg, unblinded pharmacy staff) should have access to the products used in this study.

The site is responsible for reporting any mRNA-1325 Injection that was not temperature controlled during shipment or during storage to the unblinded site (pharmacy) monitor. Such mRNA-1325 will be retained for inspection by the unblinded monitor and disposed of according to approved methods.

3.4.4.2 Study Drug Accountability

It is the investigator's responsibility that the unblinded pharmacy personnel maintain accurate records of receipt of all mRNA-1325 Injection, including dates of receipt. In addition, accurate records will be kept regarding when and how much mRNA-1325 is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all mRNA-1325 Injection will be reconciled and retained until study conclusion. At that time, mRNA-1325 Injection will be destroyed or returned to the Sponsor according to applicable regulations.

3.4.5 Blinding

This is an observer-blind study. The investigator, study subjects, site monitors, and study site personnel will be blinded to the study drug administered, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to drug accountability procedures and to prepare and administer mRNA-1325 (or placebo) to all subjects. The designee(s) will have no other study functions than study drug management, documentation, accountability, preparation, and administration. They will not be involved in subject evaluations and will not reveal the study drug identity to either the subject or the study site personnel involved in the conduct of the study, unless this information is necessary in the case of an emergency.

- An unblinded study monitor, not involved in other aspects of monitoring, will be assigned as the drug accountability monitor. They will have responsibilities to ensure the site is following all proper drug accountability, preparation, and administration procedures.

- An unblinded statistician will provide a descriptive analysis of safety and immunological endpoints after the completion of each dosing cohort. The interim analyses of immunogenicity data will be performed as outlined in Section 3.6.7.

The treatment assignment will be concealed by having the unblinded designee(s) (eg, unblinded pharmacy staff) prepare the study drug in a secure location that is not accessible to other study personnel. The syringe used will maintain the blind at the time of vaccination (eg, a sleeve will be used should the vaccine substance be distinguishable in appearance between the mRNA-1325 and placebo). Only pharmacy staff will conduct the vaccination

procedure. Once the vaccination is completed, the blinded study staff will take over further assessments and interactions with the subjects. Access to the randomization code will be strictly controlled at the pharmacy.

3.4.6 Breaking the Blind

A subject or subjects may be unblinded in the event of an SAE or other event, or if there is a medical emergency requiring the identity of the drug to be known to properly treat a subject. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 3.6.7.

3.4.7 Treatment Compliance

All doses of study drug will be administered at the study site under direct observation of study site personnel and appropriately recorded (date and time) in the eCRF. Site personnel will confirm that the subject has received the entire dose of study drug. If a subject does not receive study drug or does not receive all of the planned doses, the reason for the missed dose will be recorded.

Subjects that miss the second vaccination due to noncompliance with the visit schedule and not due to a cohort pause will still be required to follow the original visit and testing schedule. These subjects will be asked to undergo blood collection to comply with a second immune test at Visit 7 (56+7 days after first vaccination).

The study site is responsible for ensuring subjects comply with the study windows allowed. Should a subject miss a visit, every effort will be made to contact the subject and achieve a visit within the defined visit window. If a subject exceeds their post-vaccination visit in excess of 28 days from the scheduled visit or misses a vaccination schedule by more than 28 days (eg,

28 days beyond the scheduled time of vaccination), then that visit will be classified as a missed visit and the subject will continue with subsequent visits for Parts A and B of the study. All safety requirements of the missed visit will be captured and included in the follow-up visit (eg, safety laboratory testing, memory aid review for reactogenicity, immune testing, as applicable).

3.4.8 Prior and Concomitant Medications

3.4.8.1 Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the subject within the 30 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the subject's eCRF.

3.4.8.2 Concomitant Medications and Therapies

In Part A of the study, concomitant medications include all medications (including vaccination outside of trial) taken by the subject from the time of signing the informed consent form (ICF) through 28 days after the second vaccination (Visit 7) and will be recorded in the eCRF. In Part B, receipt of immunomodulators (including vaccines), immunosuppressants, or other concomitant medications that could potentially impact immune response will be collected through Visit 19.

Subjects are prohibited from receiving immunoglobulins and/or any blood products within the 3 months preceding the administration of the study drug or at any time during the study. Acetaminophen may be allowed at the discretion of the investigator. A daily dose of ≤100 mg of aspirin given under the guidance of a physician is not a contraindication to enrollment.

To allow accurate assessment of analgesic/antipyretic use during the 7 days after each vaccination, subjects will be inquired directly as to use (absent or present) and if used will be inquired for treatment or prophylaxis.

Chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune modifying drug within 6 months prior to vaccine administration or any such products during the active vaccination period (through 4 weeks after their last planned vaccination) is prohibited. An immunosuppressant dose of a glucocorticoid will be defined as a systemic dose of ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

Subjects are ineligible for the study if they have received (at any time) a vaccine for ZikaV or dengue vaccine, any live attenuated vaccines within 4 weeks before enrollment, or inactive vaccines within 2 weeks before enrollment, or plan to receive any vaccine during the active vaccination period (through 4 weeks after their last planned vaccination).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If prohibited drug therapy is taken, a joint decision will be made by the investigator and the Sponsor to continue or withhold further vaccination of the subject based on the time the medication was administered and its pharmacology and pharmacokinetics, and whether the use of the medication will compromise the subject safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medication are adequately recorded in the eCRF.

3.5 Study Procedures

Before performing any study procedures, all potential subjects will sign an ICF. The investigator must address all questions raised by the subject before the subject signs the ICF. The investigator will also sign the ICF. Subjects will undergo study procedures at the time points specified in the schedules of events (Table 6-1 and Table 6-2).

At any time during the study a subject can be seen for an unscheduled visit. This may be prompted by abnormal laboratory test results, reactogenicity issues, or new or ongoing AEs. The site also has the discretion to make reminder phone calls or text messages to inform the subject on visits, request further laboratory assessments, review memory aid content requirements, and follow up on ongoing or outstanding issues. As standard practice, a reminder call will be made to the subject by the site at least once during the first 7 days following each vaccination to ensure that the memory aid is being completed correctly and consistently.

Specific activities for each visit are outlined in Table 6-1 and Table 6-2 and may include the following:

- Confirm subject identification and contact information
- Record vital signs (toxicity scored) and perform physical examination
- Review memory aid

- Grade reactogenicity
- Assess for new AEs and follow-up on any outstanding AEs (including grading and relatedness)
- Review any new laboratory test results (toxicity scored) and identify any laboratory tests that should be repeated
- Record any concomitant medications and vaccinations since last visit
- Collect blood samples as indicated by visit
- Vaccinate (Visits 1 and 4 only)
- Schedule follow-up appointments
- Complete all eCRFs
- Enroll subject in the continued blinded follow-up period (Part B) (after subject has returned for Visit 7 [28 days following the second vaccination] in Part A)

3.5.1 Safety Contact

Once entered into Part B, each safety contact will occur by telemedicine (eg, telephone, text message, internet), and blood samples for immune persistence will be collected from each subject at the time points indicated in Table 6-2.

Safety contacts must be performed by appropriately trained study site staff. If the initial contact is unsuccessful, the study site staff should make a total of 3 attempts for each scheduled safety contact. All attempts to contact the subjects will be recorded in the source documents. The safety contact is considered missed if there is a failure to contact the subject by the time of the succeeding visit (every 28 days plus window allowance).

These contacts will follow a script, which will facilitate the collection of relevant safety information. Each safety contact will capture outcomes of any AESI or SAE that remains unresolved since the last visit or is newly identified through scripted query. Additional data may be requested through medically attended visits, and medications and vaccination will be recorded as part of the medical intake for each telemedicine visit. All safety information

described by the subject must be documented in the source documents and not documented on the script used for the safety contact.

3.5.2 Completion of Memory Aid

The memory aid utilized will be a diary card (paper) and is a method to record systematic collection of AE information from the subject; this information is subject to potential change based on further questioning and/or follow-up by study staff. Each subject will be instructed to complete a memory aid to describe:

- Solicited local and systemic AEs (Section 3.5.6) occurring (with appropriate documentation to allow severity scoring by the investigator) during the day of each dose administration and for the following 7 days
    - Daily oral body temperature measurement is to be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading will be recorded.
    - For solicited local AEs that require measurement, the measurement of size will be performed using the ruler provided by the study site.
- All medications (excluding vitamins and minerals) taken during the day of each vaccine administration and for the following 28 days
- Any unsolicited AE during the first 28 days following each vaccination

Study staff will review the information regarding solicited and unsolicited AEs, body temperature, and concomitant medications during the clinic visit. This information will be recorded in the subject's source documents and the eCRF.

3.5.3 Immunogenicity Assessments

Blood samples for immunogenicity (cellular and humoral) assessments will be collected at the time points indicated (Table 6-1 and Table 6-2). Sample aliquots will be designed so as to ensure that back up samples are available and adequate vial volumes will allow for testing needs. The actual time and date of each sample collected will be recorded in the eCRF and unique sample identification will be utilized to maintain the blind at the laboratory at all times

and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements will be provided in a separate laboratory manual.

Immunogenicity endpoints are provided in Section 3.6.2.

3.5.4 Total Blood Volume

The approximate blood volumes to be collected from each subject during the study are provided in Table 3-1.

Table 3-1 Total Blood Volume

Assessment	Blood Volume per Sample	Scheduled Number of Collections[a]	Total Amount of Scheduled Blood
Clinical Laboratory Assessments			
Hematology	2 mL	6	12 mL
Serum chemistry	6.5 mL	9	58.5 mL
Coagulation	3 mL	9	27 mL
West Nile virus	2.5 mL	1	2.5 mL
Serology[b]	6 mL	1	6 mL
Immunogenicity Assessments			
ZikaV-specific neutralizing antibody titers measured by PRNT50[c]	10 mL	5	50 mL
ZikaV antigen-specific stimulation of T cells measured by IFNγ ELISPOT on subject-derived PBMCs	40 mL	3	120 mL
ZikaV exploratory testing[c]	10 mL	5	50 mL
Subject Total			**326 mL**

Abbreviations: ELISPOT, enzyme-linked ImmunoSpot; HIV, human immunodeficiency virus; IFNγ, interferon gamma; PBMC, peripheral blood mononuclear cell; PRNT50, Plaque Reduction Neutralizing Titer EC50; YF, yellow fever; ZikaV, Zika virus.

[a] Additional blood collections may be required at the discretion of the investigator to follow up on abnormal results.

[b] Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and HIV virus type 1 and 2 antibodies. A separate counseling and consenting for HIV testing will occur.

[c] For the PRNT50 and ZikaV exploratory testing, 3 samples will be collected during Part A of the study (Visits 1, 4, and 7), and 2 samples will be collected during Part B of the study (Visits 12 and 19).

3.5.5 Safety Assessments

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs; SAEs, AESIs, AEs leading to study withdrawal, medically attended AEs, clinical laboratory test results including hematology, serum chemistry, coagulation, and urinalysis; vital sign measurements; and physical examination findings.

3.5.6 Solicited Safety Measurements

The term "reactogenicity" refers to selected signs and symptoms (AEs) occurring after dose administration, to be collected by the subject during the day of each dose administration and for the following 7 days using self-reporting and the memory aid. Subjects will be instructed to call or return to the clinic within 24 hours if a reactogenicity score reaches Grade 3 or greater during the first 7 days following vaccination.

The following AEs are included in the memory aid:

Solicited local AEs include:

- injection site induration/swelling
- injection site tenderness
- injection site erythema/redness
- injection site pain

Solicited systemic AEs include:

- body temperature (oral)
- generalized myalgia (muscle ache or pain)
- generalized arthralgia (joint ache or pain)
- headache
- fatigue/malaise (unusual tiredness)

- nausea/vomiting
- diarrhea

The solicited AEs will be recorded daily by subjects using the memory aid; where appropriate reactogenicity measurements will be taken using the tools provided (oral thermometer and measuring device). The investigator will later review, confirm, and grade reactogenicity, according to the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Center for Biologics Evaluation and Research [CBER] 2007; Table 6-3). If a solicited local or systemic AE continues beyond 7 days after dose administration, it will also be recorded as an AE in the eCRF from 8 days after vaccination until resolved or stable.

Other solicited reactions:

Use of analgesics and/or antipyretics will be recorded as absent or present, and it will be indicated if they were used for treatment or for prophylaxis.

Solicited local and systemic AEs (including body temperature) will be collected using the memory aid during the day of each dose administration and for the following 7 days. To improve recall for the next visit, subjects will record incidence of unsolicited AEs and any medication (prescription and over the counter) using the memory aid for 28 days after each vaccine administration.

All AEs necessitating an unscheduled physician visit, medical attention, or leading to withdrawal from the study will also be collected throughout Part A of the study, and all AEs will be monitored until resolution or, if the AE becomes chronic, a cause is identified. If an AE is unresolved at the conclusion of Part A of the study, a clinical assessment will be made by the investigator and the medical monitor to determine whether or not continued follow-up of the AE is warranted. The relationship of the study drug to any AE and any SAE will be determined by the investigator as related or not related. All AEs resulting in withdrawal of the subjects from the study will be documented in the source documents and in the eCRF.

For Part B of the study, a script will be utilized to query for any new SAEs or AESIs, and proper documentation will be obtained to allow an assessment of relatedness to vaccination or study participation. All SAEs and AESIs will be followed to resolution, to chronic stable state,

or until the last subject visit for Part B occurs. At that time, any ongoing AEs will receive their final classification so that the safety database can be locked.

A tabulation of all SAEs and AESIs, categorized by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and assessed relationship to study drug, will be performed.

3.5.7 Unsolicited Safety Measurements

3.5.7.1 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

3.5.7.1.1 Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to record any AEs (solicited or unsolicited) in the memory aid.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study drug. An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there are reasons to conclude that the drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator's brochure or at the specificity or severity that has been observed with the study drug being tested; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator's brochure referred only to elevated hepatic

enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator's brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Unsolicited AEs will also be evaluated by the investigator for the coexistence of any of the other following conditions:

- Medically attended AE: an AE that leads to an unscheduled visit to a healthcare practitioner

Any solicited AE that meets any of the following criteria must be entered as an AE in the AE page in the database:

- Laboratory test or vital sign measurements with a toxicity score of Grade 3 or greater
- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator
- Solicited local or systemic AE lasting beyond 7 days post-vaccination
- Solicited local or systemic AE that lead to subject withdrawal from study drug
- Solicited local or systemic AE that otherwise meets the definition of an SAE

3.5.7.1.2 Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly or birth defect
- Other medically important event

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any SAE through the agreed upon reporting mechanism.

3.5.7.1.3 Adverse Events of Special Interest

Certain AESIs are evaluated after the administration of immunostimulatory agents. All subjects enrolled in the study will be monitored for AESIs from enrollment through the end-of-study (EOS) visit. The occurrence of any of these AEs will be treated as an SAE, meeting the criterion of a "medically important event."

The list of AESIs is presented in Section 6.2.

A diagnosis of an AESI will be reported to the Sponsor in an expedited manner similar to an SAE. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's eCRF.

3.5.7.1.4 Pregnancy

The investigator is required to inform the Sponsor about any unexpected case of pregnancy occurring during the study (for female subjects), monitor the pregnancy until delivery, and report whatever outcome to the Sponsor (no later than 1 week after becoming aware of the pregnancy).

Pregnancy report forms will be distributed to the study site to be used for this purpose.

The investigator must immediately (within 24 hours of awareness) report to the Sponsor any case of pregnancy resulting in an abnormal outcome (miscarriage or newborn with congenital abnormality and/or stillbirth) according to the procedures described for SAEs.

3.5.7.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to Moderna Therapeutics, Inc. In Part A of the study, AEs will be assessed from the time of the first dose administration at Visit 1 through Visit 7. However, for the time period after the ICF is signed until before receiving the study drug, AEs will only be recorded when they are defined as one or more of the following: SAEs, AESIs, or AEs leading to study withdrawal. In Part B of the study, AESIs and SAEs will be assessed from Visit 8 through Visit 19. Any AEs occurring before receipt of the study drug will be analyzed separately from TEAEs.

At every clinic visit or telephone contact, subjects will be asked a standard question to elicit any medically related changes in their well-being according to the scripts provided. Subjects will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, data from clinical laboratory test results, physical examination findings, or other documents relevant to subject safety classified as an AE will be documented on the AE page of the eCRF.

3.5.7.3 Reporting Adverse Events

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment and dose, type of event, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The MedDRA will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

Any AE considered serious by the investigator or which meets SAE criteria (Section 3.5.7.1.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

The following contact information is to be used for SAE reporting:

SAE Hotline: PPD
SAE Fax line: PPD

3.5.7.4 Assessment of Severity of Unsolicited Adverse Events

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities and will be classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4) using the following criteria:

- Mild (Grade 1): These events do not interfere with the subject's daily activities.
- Moderate (Grade 2): These events cause some interference with the subject's daily activities but do not require medical intervention.
- Severe (Grade 3): These events prevent the subject's daily activity and require medical intervention.
- Life threatening (Grade 4): These events require an emergency room visit or hospitalization.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (CBER 2007) will be used to categorize solicited

reactogenicity, safety laboratory test results, and vital sign measurements observed during this study. Specific criteria for clinical and laboratory abnormalities are presented in Table 6-3 and Table 6-4, respectively, and will be graded if outside of the reference range for the laboratory utilized. Of note, the laboratory test value itself may not be the AE classification. Each AE will be classified by its most specific term (eg, renal insufficiency, bronchitis) and supporting evidence (eg, laboratory test value, x-ray) will not be classified as an AE per se.

3.5.7.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: There is not a reasonable possibility of Sponsor's product relationship: Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product.

- Related: There is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

3.5.7.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until the AE is resolved or stable or judged by the investigator to be not clinically significant in Part A of the study. For Part B of the study, only AESIs and SAEs will be recorded. The investigator may request an unscheduled visit at any time, if warranted.

3.5.8 Clinical Laboratory Testing

Clinical laboratory tests will be performed by the central laboratory, unless specified otherwise. Blood and urine will be collected in Part A at the time points indicated in the schedule of events (Table 6-1). Fasting is not required before collection of laboratory samples.

The following hematology, serum chemistry, urinalysis, and other laboratory assessments will be performed. The results will be toxicity scored using Table 6-4.

Hematology:	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and total and differential white blood cell count
Serum chemistry:	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, amylase, lipase, bilirubin (total and direct), blood urea nitrogen, creatinine, random glucose, potassium, sodium, total protein, albumin, and calcium Females subjects only: β-human chorionic gonadotropin (childbearing potential) and follicle-stimulating hormone (post-menopausal)
Urinalysis:	pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, leucocytes, and specific gravity
Coagulation:	Prothrombin time and partial thromboplastin time

A pregnancy test (β-human chorionic gonadotropin) will be performed on all female subjects of childbearing potential at Screening (serum pregnancy test), before each dose administration (urine pregnancy test), and as needed at unscheduled visits (serum pregnancy test). Serum pregnancy tests will be sent to the central laboratory, while urine pregnancy tests will be performed by the local laboratory on site. A follicle-stimulating hormone test will be performed at Screening, as necessary, to confirm post-menopausal status in female subjects, if not documented in the subject's medical records.

Human immunodeficiency virus (types 1 or 2) antibody, hepatitis B surface antigen, and hepatitis C virus antibody will be assessed at Screening.

At Screening, if the subject has no proof of yellow fever vaccination within 20 years, or other documentation of flavivirus status, the West Nile virus screening test will be administered. A West Nile virus serology screen can occur up to 90 days prior to randomization.

A urine screen for drugs of abuse will be performed by the local laboratory at Screening and before dose administration at Visit 1 for opiates, cocaine, phencyclidine, amphetamines, benzodiazepines, and methadone (cannabis excluded).

Should safety laboratory testing at 7 days post-vaccination result in a Grade 2 or greater toxicity score, then repeat testing within the next 10 days must occur and this may include an unscheduled visit. Should the subject's laboratory test value not return to Baseline then periodic testing may be needed until the abnormality is deemed to be associated with a new stable AE or determined to be not clinically significant by the investigator.

Those values that fall within the normal range of the laboratory will automatically be classified as normal and receive a toxicity score of 0. All values that have a toxicity score of Grade 1 or greater will also be evaluated by the investigator and classified as "abnormal clinically significant (CS)", or "abnormal not clinically significant (NCS)." Investigators should use their clinical judgment when considering the clinical significance of any abnormal laboratory findings. All laboratory test values with a toxicity score of Grade 3 or greater will be entered as AEs. Any additional laboratory test value that is determined to be clinically significant will also be recorded as an AE, should that be considered the primary diagnosis. In such instances, the abnormal value and grade will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached the reference range or the values at Screening or until the investigator determines that follow-up is no longer medically necessary. The only exception to this rule would be a laboratory test value that is associated with an identified ongoing AE where that event would be the classifying AE.

3.5.9 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature (which is classified as a solicited systemic event). The subject will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured in Part A at the time points indicated in the schedule of events (Table 6-1).

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities (Table 6-3) of Grade 3 or higher, the abnormal value and grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality and that would result in an AE classification). The investigator will continue to monitor the subject with additional assessments until the value has reached the reference range,

the value at Screening, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

3.5.10 Physical Examinations

In Part A, a full physical examination will be performed at Screening and a symptom-directed (targeted) physical examination will be performed at all other scheduled time points indicated in the schedule of events (Table 6-1). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Prior to vaccination and at 7 days following vaccination, a physical evaluation of the arm that was vaccinated and the associated lymph nodes should be evaluated.

Height and weight will be measured and body mass index will be calculated at Screening only.

3.6 Statistical Analysis Plans

3.6.1 Safety Endpoints

The following are the safety (primary) endpoints:

Part A:

- Solicited AEs with toxicity scoring (local and systemic reactogenicity events) collected for 7 days following each vaccination
- Unsolicited AEs collected for 28 days following each vaccination; additional classification if serious, medically attended, leading to study withdrawal, or an AESI
- Safety laboratory test results with toxicity scoring (hematology, serum chemistry, and coagulation) collected at Baseline and 7 (+3) days and 28 (+7) days following each vaccination
- Urinalysis test results with toxicity scoring collected at Baseline and 7 (+3) days following each vaccination

- A subset of safety laboratory test results (as specified in Table 6-1) with toxicity scoring collected additionally at 17 (±3) days following each vaccination and 21 (+3) days (sentinel subjects) following the first vaccination

- Vital sign measurements with toxicity scoring on day of vaccination and 7 and 28 days following each vaccination

Part B:

- AESIs and SAEs through 1 year (or until resolved, whichever occurs first) following the last vaccination

3.6.2 Immunogenicity Endpoints

The immunogenicity assessments (cellular and humoral) are as follows:

Part A:

- Neutralizing serum antibody titers (PRNT50) to Zika (Baseline [pre-vaccination at Visit 1] and at 28 days following each vaccination [Visits 4 and 7, respectively])

- Neutralizing serum antibody titers (PRNT50) to yellow fever (Baseline [pre-vaccination at Visit 1] and at 28 days following each vaccination [Visits 4 and 7, respectively]) in the flavivirus-seropositive group

- T-cell response (cytokine activation to IFNγ or other cytokines) (Baseline [pre-vaccination at Visit 1] and at 7 days following each vaccination [Visits 2 and 5, respectively]), if results of interim immunogenicity analyses warrant further analyses of samples.

Part B:

3.6.3 Neutralizing serum antibody titers (PRNT50) to Zika virus at 168 (±15) days and 364 (+15) days (Visits 12 and 19, respectively) following the second vaccination will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence. Sample Size Calculations

Approximately 90 subjects are planned to be randomly assigned to receive study treatment. Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and is considered sufficient to meet the study objectives of identifying a dose and establishing initial safety results in a population of healthy adults in a non-endemic Zika region.

3.6.4 Analysis Sets

The All Enrolled Subjects set will include subjects who signed the ICF. The All Enrolled Subjects set will only be used for descriptive purposes.

The Safety set will include all subjects who receive at least 1 dose of study drug (mRNA-1325 or placebo). All subjects in the Safety set will be analyzed according to the study drug actually received and not according to the study drug the subject was randomized to receive, in the event there is a discrepancy.

The Per-Protocol set will include all subjects who did not observe a major protocol violation, received vaccine within the acceptable vaccination window (their full dose[s] of assigned study drug), had blood collection within accepted visit windows, and had a pre-vaccination and at least 1 serum sample from the post-vaccination testing period available for testing. All subjects in the Per-Protocol set will be analyzed according to the study drug the subject was randomized to receive and not according to what was actually received, in the event there is a discrepancy. In the case where there is not a paired sample for the specific time point that data will not be included in the analysis.

The Intent-to-Treat set will provide supportive analyses. For the Intent-to-Treat set, all subjects who were randomized to the study will be included regardless of protocol violations, exceeded visit windows, missed vaccination, or missing data.

3.6.5 Statistical Analysis

Details of all statistical analyses will be described in a statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics.

Data from subjects who received placebo will be pooled across cohorts for all treatments.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

3.6.5.1 Immunogenicity Analyses

The following immunogenicity outcome measures (for serum neutralizing antibody titers) and their 95% CIs, where appropriate, will be summarized by treatment group and by visits after each vaccination:

- Geometric mean titer (GMT) of anti-Zika virus neutralizing antibodies (PRNT50 assay)
    - Part A: At Baseline (pre-vaccination at Visit 1) and on 28 days after both first and second vaccination (Visits 4 and 7, respectively)
    - Part B: At 168 (±15) days and 364 (+15) days (Visits 12 and 19, respectively) will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence.
- Geometric mean ratio $(GMR)_{Post/Pre}$
    - Part A and Part B: The ratio of post-vaccination GMT to pre-vaccination (Visit 1) GMT of subjects who have a baseline sample (pre-vaccination at Visit 1) and post-vaccination sample at any post-dose time point (Visits 4, 7, 12, or 19; data from visits 12 and 19 will be included only if based on interim immunogenicity analyses results the evaluation of these later timepoints is warranted.)
- Seroconversion

- Part A: The proportion of subjects with Zika virus PRNT50 titer ≥1:10, ≥1:20, ≥1:40, ≥1:80, ≥1:160, and ≥1:320 at Baseline, Visit 4, and Visit 7

- Part A: The proportion of subjects with baseline Zika virus PRNT50 titer <1:10 and post-vaccination Zika virus PRNT50 titer of ≥1:20; or with baseline Zika virus PRNT50 titer ≥1:10 and with post-vaccination 4-fold titer increase (Visits 4 or 7)

- Part B: The proportion of subjects who maintained seroconversion status at specific time points of 168 (±15) days and 364 (+15) days (Visits 12 and 19, respectively). Data from visits 12 and 19 will be included only if based on interim immunogenicity analyses results the evaluation of these later timepoints is warranted.

- Cross-Stimulation with prior flavivirus vaccination (subset of flavivirus-seropositive subjects)

  - Part A:

  - Geometric mean titer (GMT) of anti-yellow fever neutralizing antibodies at Baseline, Visit 4, and Visit 7

  - Geometric mean ratio (Post/Pre) of anti-yellow fever neutralizing antibodies at Visit 4 and Visit 7

  - The proportion of subjects with anti-yellow fever antibody titer ≥1:10, ≥1:20, ≥1:40, ≥1:80, ≥1:160, and ≥1:320 at Baseline, Visit 4, and Visit 7

  - Additional neutralization assays for other flavivirus may be performed in select subsets

3.6.5.2 Safety Analyses

Data from subjects who received placebo will be pooled across cohorts for all treatments. Reactogenicity will be summarized by treatment assignment (10-, 25-, or 100-µg mRNA-1325 or placebo), vaccination (first or second), duration, and severity. Adverse events will be coded by preferred term and system organ class using MedDRA and summarized by part, treatment assignment, vaccination (first or second), and overall. Adverse events will also be summarized by severity and relationship to the study vaccine. Descriptive statistics will be presented and the difference in the proportion of subjects with AEs will be provided comparing each dose

level with placebo recipients across all groups. Individual subject listings will be provided for all AEs, AEs leading to study withdrawal, AESIs, medically attended AEs, and SAEs.

Safety data from clinical laboratory test results and vital sign measurements will be graded by severity scoring and analyzed by treatment group and vaccination (first or second). Absolute and change from baseline values will be provided according to the toxicity table, along with mean, median, and standard deviation. Results of serology, urine drug screen, and pregnancy tests will be listed for all subjects randomly assigned to receive study treatment.

Medical history data for all subjects randomly assigned to receive study treatment will be presented by subject in a listing.

Baseline demographic and background variables will be summarized by treatment group and cohort for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

Prior and concomitant medication will be listed (with start and stop dates) for each subject and summarized by common medical dictionary coding. Any vaccinations that occur during the trial conduct will also be captured and summarized.

3.6.6 Handling of Missing Data

For GMT calculation, antibody values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. For fold-rise, values <LLOQ will be replaced by 0.5 × LLOQ for a numerator and by LLOQ for a denominator. If both the numerator and denominator are <LLOQ, then both will be converted in the same way. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

3.6.7 Interim Analyses

Following completion of each cohort in Part A, the database will be locked for that cohort and safety and immune test results will be analyzed through 28 days following the second vaccination. As dose escalation occurs, cumulative analyses will be included for each subsequent data lock to allow for all prior dosing cohorts to be analyzed by cohort, treatment

assignment, and in aggregate for mRNA-1325 exposure. Immunogenicity and safety data, including mean group analyses of change from Baseline, where applicable, will be summarized for each dose cohort. These data are required to inform decisions on dose selection for this and other development programs using the same mRNA platform. Subject-level treatment assignment will not be released to the subjects or to those individuals involved in managing or assessing safety in Part B of the study until that portion of the study is completed.

Additional information can be found in the statistical analysis plan.

3.7 Data Quality Assurance

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current ICH harmonised tripartite guideline E6(R1): Good Clinical Practice and current standard operating procedures. The eCRFs will be utilized and accessed through iMedidata® via the internet. This electronic data capture system is validated and compliant with US Title 21 of CFR Part 11. Each person involved with the study will have an individual identification code and password that allow for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Due to safety review requirements, no more than 3 business days should transpire between subject data availability (visits, laboratory test results, etc) and data entry. As a quality measure, timeliness of data entry and data query resolution will be reported to the IST. Other issues of data quality that may hinder safety review or pose a concern with patient safety will also be reported to the IST with appropriate awareness to the SMC if needed.

4 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

4.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

4.2 Institutional Review

Federal regulations and the ICH E6(R1) guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R1) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both and the date approval or a favorable opinion was granted.

4.3 Subject Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before he or she enters the study or before any unusual or non-routine procedure that involves risk to the subject are performed. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give his or her consent to participate in the study by signing the ICF. A separate counseling and consent for HIV testing will occur.

The ICF will also explain that excess serum from immunogenicity testing may be used for future research which may be performed at the discretion of the Sponsor to better characterize the immune response to the ZikaV protein (inclusive of further T- and B-cell responses, additional assay development, and the immune response across flaviviruses).

The investigator or designee will provide a copy of the ICF to the subject. The original form shall be maintained in the subject's medical records at the site.

4.4 Study Reporting Requirements

By participating in this study the investigator agrees to submit reports of SAEs and AESIs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

4.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor, PPD, nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor, PPD, nor the study site is financially responsible for further treatment of the disease under study.

4.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval,
- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current,
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study,
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject, and
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

4.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all

national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current Good Clinical Practice guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

4.8 Data Collection

4.8.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

Electronic case report forms are accessed through iMedidata® via the internet. This electronic data capture system is validated and compliant with 21 CFR 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

4.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

4.10 Reporting Adverse Events

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his IRB as appropriate. The investigator also agrees to provide the Sponsor

with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

4.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome, and the Sponsor and regulatory authority(ies) with any reports required.

4.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

4.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without their prior authorization, but data and publication thereof will not be unduly withheld.

5 Study Management

5.1 Monitoring

5.1.1 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The monitor will be blinded to treatment assignment. A separate unblinded study monitor will be responsible for drug accountability.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R1) guidelines and standard operating procedures.

5.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

5.2 Management of Protocol Amendments and Deviations

5.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects are enrolled into an amended protocol.

5.2.2 Protocol Violations and Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when the subject or investigator do not adhere to the protocol, resulting in a significant, additional risk to the subject. Protocol violations can include non-adherence to inclusion or exclusion criteria, enrollment of the subject without prior Sponsor approval, or non-adherence to FDA regulations or ICH E6(R1) guidelines.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of violations and deviations. The IRB should be notified of all protocol violations and deviations, if appropriate, in a timely manner.

5.3 Study Termination

Although the Sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the clinical study report.

5.4 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and have the opportunity to review complete study results.

A final clinical study report will contain all data collected through 28 days following the second vaccination (Part A) and all data from the extension safety period through the 12-month follow-up after the second vaccination (Part B) of all dosing cohorts.

Upon completion of the clinical study report, the Sponsor will provide the investigator(s) with the final approved clinical study report.

6 Appendices

6.1 Appendix 1: Schedules of Events

The schedule of events for Part A is presented in Table 6-1 and the schedule of events for Part B is presented in Table 6-2.

Table 6-1 Part A: Schedule of Events

Procedure	**Screening**	**Treatment Period**							
Study visit	**0**	**1**	**2**	**3**	**3a[a]**	**4**	**5**	**6**	**7**
Vaccination Day		**X**				**X**			
Days relative to most recent vaccination	**N/A**	**0**	**7**	**17**	**21**	**28**	**7**	**17**	**28**
Window allowance	**+28**	**0**	**+3**	**±3**	**+3**	**+7**	**+3**	**±3**	**+7**
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history	X								
Follicle-stimulating hormone (female subjects only)[b]	X								
Serology[c]	X								
West Nile virus screen (ONLY if no proof of yellow fever vaccination or flavivirus status)[d]	X								
Urine drug screen[e]	X	X							
Physical examination[f]	X	X	X		X	X	X		X
Vital sign measurements[g]	X	X/Xc	X		X	X/Xc	X		X
Safety laboratory tests	X[h]	X[h]	X[h]	X[i]	X[i]	X[h]	X[h]	X[i]	X[h]
Urinalysis[j]	X	X	X			X	X		
Pregnancy test (female subjects of childbearing potential)[k]	X	X				X			
Randomization		X							
Immune testing (cellular) (PBMC ELISPOT assay)		X[l]	X				X		
Immune testing (humoral) (PRNT50 neutralization assay) and ZikaV exploratory testing		X[l]				X[l]			X
Vaccination[m]		X				X			
Reactogenicity		X/Xc	X		X	X/Xc	X		
Provision and instruction on memory aid (and tools provided)[n]		X				X			
Subject memory aid review: solicited local and systemic AEs, oral body temperature, and medications taken			X		X		X		

Procedure	**Screening**	**Treatment Period**							
Study visit	**0**	**1**	**2**	**3**	**3a[a]**	**4**	**5**	**6**	**7**
Vaccination Day		**X**				**X**			
Days relative to most recent vaccination	**N/A**	**0**	**7**	**17**	**21**	**28**	**7**	**17**	**28**
Window allowance	**+28**	**0**	**+3**	**±3**	**+3**	**+7**	**+3**	**±3**	**+7**
Subject memory aid review: any unsolicited AEs and related medications			X		X	X	X		X
Collection of memory aid						X			X
All unsolicited AEs (including SAEs, medically attended, leading to study withdrawal, or AESI)[o]		X	X	X	X	X	X	X	X
Concomitant medications[p]	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ELISPOT, enzyme-linked ImmunoSpot; N/A, not applicable; PBMC, peripheral blood mononuclear cell; PRNT50, Plaque Reduction Neutralizing Titer EC50; SAE, serious adverse event.

Childbearing potential defined as any female who has experienced menarche and who is NOT permanently sterile or post-menopausal. Post-menopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

Note: X/Xc denotes being performed before and after vaccination.

[a] Visit 3a will comprise of sentinel cohort only.

[b] To confirm post-menopausal status, as needed.

[c] Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus type 1 and 2 antibodies.

[d] At Screening, if the subject has no proof of yellow fever vaccination within 20 years, or other documentation of flavivirus status, the West Nile virus screening test will be administered. West Nile virus serology screen can occur up to 90 days prior to randomization.

[e] Urine drug screen for drugs of abuse will be performed at Screening and before dose administration at Visit 1 for opiates, cocaine, phencyclidine, amphetamines, benzodiazepines, and methadone (cannabis excluded).

[f] Full physical examination at Screening; symptom-directed (targeted) physical examination at all other scheduled time points. Interim physical examinations will be performed at the discretion of the investigator, if necessary. Height and weight will be measured and body mass index calculated at Screening only.

[g] Vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) at Visit 1 and Visit 4 will be collected once before dose administration and at least 60 minutes after dose administration (before subjects are discharged).

[h] Safety laboratory test values include hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, total and differential white blood cell count, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, amylase, lipase, bilirubin (total and direct), blood urea nitrogen, creatinine, random glucose, potassium, sodium, total protein, calcium, albumin, prothrombin time, partial thromboplastin time.

[i] A subset of safety laboratory test values for albumin, bilirubin (total and direct), prothrombin time, partial thromboplastin time, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase.

[j] Urinalysis parameters include pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, leucocytes, and specific gravity.

[k] A pregnancy test will be performed at Screening (serum pregnancy test), before each dose administration (urine pregnancy test), and as needed at unscheduled visits (serum pregnancy test). Serum pregnancy tests will be sent to the central laboratory, while urine pregnancy tests will be performed by the local laboratory on site.

[l] To occur prior to vaccination.

[m] Vaccination cannot occur if vitals are ≥Grade 2, or if a subject has an intercurrent illness (including a fever). Each subject will be monitored in the clinic for at least 1 hour following vaccination to assess for immediate reactogenicity, with vital sign measurements and local and systemic reactogenicity toxicity scored at least 60 minutes following the vaccination (and earlier if deemed necessary by the investigator).

[n] Subjects will be instructed on recording reactogenicity, AEs, and medications (prescription or over-the-counter) on the memory aid (ie, diary card), and will be provided measuring tools, and instructed to call or return to the clinic within 24 hours if a reactogenicity score reaches Grade 3 or greater during the first 7 days following vaccination. The site will make a reminder call to the subject during the first 7 days (at approximately Day 4) post-vaccination to ensure that the memory aid is being completed correctly and consistently.

[o] In Part A of the study, AEs will be assessed from the time of the first dose administration at Visit 1 through Visit 7. However, for the time period after the informed consent form is signed until before receiving the study drug, AEs will only be recorded when they are defined as one or more of the following: SAEs, AEs of special interest, or AEs leading to study withdrawal.

[p] Concomitant medications include all medications (including vaccination outside of trial) taken by the subject from the time of signing the informed consent form through 28 days after the second vaccination (Visit 7).

Table 6-2 Part B: Schedule of Events

Procedure												
Study visit[a]	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study day from 1st dose, if 2nd dose not completed	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**
Study day from 2nd dose, if completed	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Window allowance	**±7**	**±7**	**±7**	**±7**	**±15**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**+15**
Safety contact	X	X	X	X	X	X	X	X	X	X	X	X
Immune testing (humoral) and ZikaV exploratory testing[b]					X							X
AESIs[c]	X	X	X	X	X	X	X	X	X	X	X	X
SAEs[c]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[d]	X	X	X	X	X	X	X	X	X	X	X	X
EOS visit												X

Abbreviations: AESI, adverse event of special interest; EOS, end of study; SAE, serious adverse event.

[a] Each safety contact in Part B will occur by telemedicine (eg, telephone, text message, internet) and blood samples will be collected as described in footnote b.

[b] Blood samples for immune persistence will be collected from each subject at 168 (±15) days and 364 (+15) days following the second vaccination. Immune persistence at 168 days and 364 days will be evaluated if interim immunogenicity analyses warrants long term analyses of persistence.

[c] Each safety contact will capture outcomes of any AESI or SAE that remains unresolved since the last visit or is newly identified through scripted query. Additional data may be requested through medically attended visits, and medications and vaccination will be recorded as part of the medical intake for each telemedicine visit.

[d] Receipt of immunomodulators (including vaccines), immunosuppressants, or other concomitant medications that could potentially impact immune response will be collected through Visit 19.

6.2 Appendix 2: Adverse Events of Special Interest

The following is a list of Adverse Events of Special Interest:

Gastrointestinal disorders:

- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders:

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases:

- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal disorders:

- Antisynthetase syndrome
- Dermatomyositis

- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuro-inflammatory disorders:

- Acute disseminated encephalomyelitis, including site specific variants (eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy

- Optic neuritis
- Transverse myelitis

Skin disorders:

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid, and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet’s syndrome
- Vitiligo

Vasculitides:

- Large vessels vasculitis including: including Takayasu's arteritis and giant cell arteritis/temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg−Strauss syndrome (allergic granulomatous angiitis), Buerger’s disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody positive vasculitis (type unspecified), Henoch−Schönlein purpura, Behcet's syndrome, and leukocytoclastic vasculitis

Others:

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis

6.3 Appendix 3: Toxicity Grading Scale Tables

The toxicity grading scales for clinical and laboratory abnormalities are presented in Table 6-3 and Table 6-4, respectively. Note that for laboratory abnormalities, grading only occurs if the values reside outside of the normal values established by the clinical laboratory. For study-specific laboratory normal ranges and associated toxicity grades, refer to the laboratory manual.

Table 6-3 Tables for Clinical Abnormalities

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

Abbreviation: ER, emergency room.

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

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

Source: Guidance for industry – Toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for clinical abnormalities (CBER 2007).

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Tachycardia (beats per minute)	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia (beats per minute)**	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths per minute)	17 – 20	21 – 25	> 25	Intubation

Abbreviation: ER, emergency room.

Note that fever is classified under systemic reactions for grading purposes.

* Subject should be at rest for all vital sign measurements.

** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Source: Guidance for industry – Toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for clinical abnormalities (CBER 2007).

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 to 2 episodes/ 24 hours	Some interference with activity or > 2 episodes/ 24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 g/ 24 hours	4 – 5 stools or 400 – 800 g/ 24 hours	6 or more watery stools or > 800 g/ 24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise (unusual tiredness)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized myalgia (muscle ache or pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Generalized arthralgia (joint ache or pain)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Abbreviations: ER, emergency room; IV, intravenous.

* Oral temperature; no recent hot or cold beverages or smoking.

Sources: Guidance for industry – Toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for clinical abnormalities (CBER 2007). DAIDS Grading the Severity of Adult and Pediatric Adverse Events (DAIDS 2014).

Table 6-4 Tables for Laboratory Abnormalities

Serum Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – hyponatremia (mEq/L)	132 – 134	130 – 131	125 – 129	< 125
Sodium – hypernatremia (mEq/L)	144 – 145	146 – 147	148 – 150	> 150
Potassium – hyperkalemia (mEq/L)	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – hypokalemia (mEq/L)	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – hypoglycemia (mg/dL)	65 – 69	55 – 64	45 – 54	< 45
Glucose – hyperglycemia Random (mg/dL)	110 – 125	126 – 200	> 200	Insulin requirements or hyperosmolar coma
Blood urea nitrogen (mg/dL)	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine (mg/dL)	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia (mg/dL)	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia (mg/dL)	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Albumin – hypoalbuminemia (g/dL)	2.8 – 3.1	2.5 – 2.7	< 2.5	–
Total Protein – hypoproteinemia (g/dL)	5.5 – 6.0	5.0 – 5.4	< 5.0	–
Alkaline phosphate; increase by factor	1.1 – 2.0 × ULN	2.1 – 3.0 × ULN	3.1 – 10 × ULN	> 10 × ULN
Liver function tests –ALT and AST; increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
Bilirubin – when accompanied by any increase in liver function test; increase by factor	1.1 – 1.25 × ULN	1.26 – 1.5 × ULN	1.51 – 1.75 × ULN	> 1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN
Pancreatic enzymes – amylase and lipase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	> 5.0 × ULN

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of the normal range.

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

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125 – 129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

Source: Guidance for industry – Toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for laboratory abnormalities (CBER 2007).

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (female) (g/dL)	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) (g/dL)	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value (g/dL)	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase (cell/mm^3)	10800 – 15000	15001 – 20000	20001 – 25000	> 25000
WBC decrease (cell/mm^3)	2500 – 3500	1500 – 2499	1000 – 1499	< 1000
Lymphocytes decrease (cell/mm^3)	750 – 1000	500 – 749	250 – 499	< 250
Neutrophils decrease (cell/mm^3)	1500 – 2000	1000 – 1499	500 – 999	< 500
Eosinophils (cell/mm^3)	650 – 1500	1501 – 5000	> 5000	Hypereosinophilic
Platelets decreased (cell/mm^3)	125 000 – 140 000	100 000 – 124 000	25000 – 99000	< 25000
PT; increase by factor	1.0 – 1.10 × ULN	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 × ULN
PTT; increase by factor	1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell.

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

Source: Guidance for industry – Toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for laboratory abnormalities (CBER 2007).

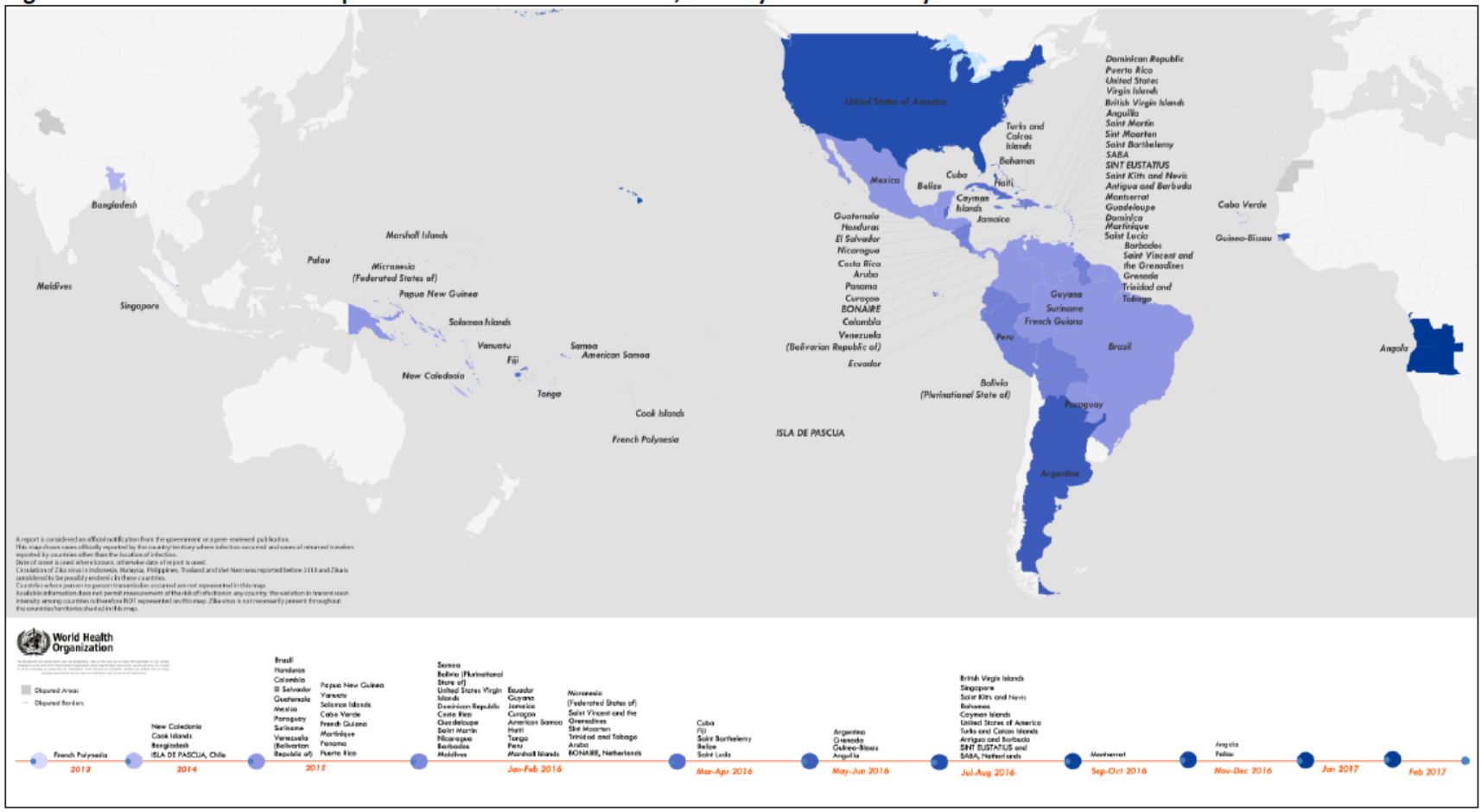
Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells transfusion

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

Source: Guidance for industry – Toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for laboratory abnormalities (CBER 2007).

6.4 Appendix 4: World Health Organization Zika Situation Report as of February 2017

Figure 2. New detection of mosquito-borne Zika virus infections, January 2013–February 2017



The WHO map (dated 01 February 2017; WHO 2017) showing Zika-endemic regions is subject to routine updating. The most up-to-date regions can be found within each situation report, including the countries and territories listing Zika virus transmission (WHO Table 1 below; WHO 2017) at: http://www.who.int/emergencies/zika-virus/situation-report/en/

Table 1. Countries and territories that have reported mosquito-borne Zika virus transmission

Classification	WHO Regional Office	Country / territory	Total
Category 1: Countries with a reported outbreak from 2015 onwards#	AFRO	Angola; Cabo Verde; Guinea-Bissau	3
	AMRO/PAHO	Anguilla; Antigua and Barbuda; Argentina; Aruba; Bahamas; Barbados; Belize; Bolivia (Plurinational State of); Bonaire, Sint Eustatius and Saba – Netherlands; Brazil; British Virgin Islands; Cayman Islands; Colombia; Costa Rica; Cuba; Curaçao; Dominica; Dominican Republic; Ecuador; El Salvador; French Guiana; Grenada; Guadeloupe; Guatemala; Guyana; Haiti; Honduras; Jamaica; Martinique; Mexico; Montserrat; Nicaragua; Panama; Paraguay; Peru; Puerto Rico; Saint Barthélemy; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Sint Maarten; Suriname; Trinidad and Tobago; Turks and Caicos; United States of America; United States Virgin Islands; Venezuela (Bolivarian Republic of)	48
	WPRO	American Samoa; Fiji; Marshall Islands; Micronesia (Federated States of); Palau; Samoa; Singapore; Tonga	8
Subtotal			59
Category 2: Countries with possible endemic transmission or evidence of local mosquito-borne Zika infections in 2016 or 2017	SEARO	Indonesia; Maldives; Thailand	3
	WPRO	Malaysia; New Caledonia; Philippines; Viet Nam	4
Subtotal			7
Category 3: Countries with evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases in 2016 or 2017, or outbreak terminated	AFRO	Gabon**	1
	PAHO/AMRO	ISLA DE PASCUA – Chile**	1
	SEARO	Bangladesh**	1
	WPRO	Cambodia**; Cook Islands**; French Polynesia**; Lao People's Democratic Republic; Papua New Guinea; Solomon Islands; Vanuatu	7
Subtotal			10
Total			76

PPD will operationalize the monitoring of the Zika-endemic changes and notify a site if they appear to be reaching the endemic listing.

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