CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose Confirmation Study to Evaluate the Safety, Tolerability, and Immunogenicity of Zika Vaccine mRNA-1893 in Adults Aged 18 Through 65 Years and Living in Endemic and Non-Endemic Flavivirus Areas
Protocol Number:	mRNA-1893-P201
Sponsor Name: **Legal Registered Address:**	ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139
Sponsor Contact:	PPD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: PPD e-mail: PPD
Regulatory Agency Identifier Number:	Investigational New Drug (IND) Number: 19088
Amendment Number:	3
Date of Amendment 3:	09 Dec 2021
Date of Amendment 2:	27 Oct 2021
Date of Amendment 1:	16 Sep 2021
Date of Original Protocol:	21 Feb 2021

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose Confirmation Study to Evaluate the Safety, Tolerability, and Immunogenicity of Zika Vaccine mRNA-1893 in Adults Aged 18 Through 65 Years and Living in Endemic and Non-Endemic Flavivirus Areas
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Protocol accepted and approved by:

See esignature and date signed on last page of document

Date

PPD

ModernaTX, Inc.
200 Technology Square
Cambridge, MA 02139
Telephone: PPD
e-mail: PPD

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled, "A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose Confirmation Study to Evaluate the Safety, Tolerability, and Immunogenicity of Zika Vaccine mRNA-1893 in Adults Aged 18 Through 65 Years and Living in Endemic and Non-Endemic Flavivirus Areas," and the most recent version of the Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP), and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB/IEC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	09 Dec 2021
Amendment 2	27 Oct 2021
Amendment 1	16 Sep 2021
Original Protocol	21 Feb 2021

Amendment 3 (09 Dec 2021): Current Amendment

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:	ModernaTX, Inc.
Name of Investigational Product:	mRNA-1893 Injection
Protocol Title:	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose Confirmation Study to Evaluate the Safety, Tolerability, and Immunogenicity of Zika Vaccine mRNA-1893 in Adults Aged 18 Through 65 Years and Living in Endemic and Non-Endemic Flavivirus Areas
Protocol Number:	mRNA-1893-P201
Study Period (Months):	Approximately 25 months
Phase of Development:	2
Study Sites:	Clinical sites in both endemic and non-endemic Zika regions
Objectives:	**Primary Objectives** • To evaluate the safety, tolerability, and reactogenicity of 2 dose levels of messenger RNA (mRNA)-1893 Zika vaccine, administered in a 1-dose (CCI µg) or 2-dose schedule (CCI µg or CCI µg dose level) given 28 days apart, in comparison to a placebo control. • To evaluate the immunogenicity of 2 dose levels of mRNA-1893 Zika vaccine, administered in a 1-dose (CCI µg) or 2-dose schedule (CCI µg orCCI µg dose level) given 28 days apart, as measured by Zika virus (ZIKV)-specific neutralization assay (plaque reduction neutralization [PRNT]), in comparison to a placebo control at Day 57. **Secondary Objectives** • To evaluate the immunogenicity of 2 dose levels of mRNA-1893, as measured by ZIKV-specific neutralization assay (PRNT and microneutralization [MN]), in comparison to a placebo control, in flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline. **Exploratory Objectives** • To evaluate the duration of the humoral immune response of 2 dose levels of mRNA-1893 at Days 85, 196, 364, 532, and 700, as measured by ZIKV-specific neutralization assay (PRNT and MN), in comparison to a placebo control, in flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline. • To evaluate the humoral immunogenicity of 2 dose levels of mRNA-1893, as measured by reporter virus particle (RVP) and by ligand binding assay, in comparison to a placebo control, in

	flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline. • To evaluate the ZIKV-specific cellular immune response of 2 dose levels of mRNA-1893 in comparison to a placebo control in flavivirus-seronegative participants at baseline and flavivirus-seropositive participants at baseline (cell-mediated immunity [CMI] subset of participants). • To assess the occurrence of flavivirus infections throughout the entire course of participation in the study in comparison to a placebo control.
Endpoints:	**Primary Safety Endpoints** • Solicited local and systemic adverse reactions (ARs) through 7 days after each investigational product (IP) injection. • Unsolicited adverse events (AEs) through 28 days after each IP injection. • Medically attended AEs (MAAEs) throughout the entire study period. • Serious AEs (SAEs) and adverse events of special interest (AESIs) throughout the entire study period. **Primary Immunogenicity Endpoints** • Geometric mean titer (GMT) of ZIKV-specific neutralizing antibodies (nAbs) at Day 57, as measured by PRNT, in all participants, in initially flavivirus-seronegative, and in initially flavivirus-seropositive participants. • Seroconversion from Day 1 to Day 57 (seroconversion is defined as either an increase in ZIKV-specific nAb titer from below the lower limit of quantification [LLOQ] to a titer equal to or above LLOQ, or an increase of at least 4-fold in ZIKV-specific nAb titer in participants with pre-existing nAb titers [as measured by PRNT]). **Secondary Immunogenicity Endpoints** • GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, and 57 (Day 57 only for MN), as measured by PRNT and MN. • GMT of ZIKV-specific nAbs in initially flavivirus-seronegative participants at Days 1, 8, 29, 36, and 57 (Day 57 only for MN), as measured by PRNT and MN. • GMT of ZIKV-specific nAbs in initially flavivirus-seropositive participants at Days 1, 8, 29, 36, and 57 (Day 57 only for MN), as measured by PRNT and MN. • Geometric mean fold rise (GMFR) of ZIKV-specific nAbs in all participants, in initially flavivirus-seronegative and in initially flavivirus-seropositive participants at Days 8, 29, 36, and 57, as measured by PRNT and MN. • Seroconversion from Day 1 (baseline) to Days 8, 29, 36, and 57 (only for MN), as measured by PRNT and MN.

- Seroresponse at Days 8, 29, 36, and 57 (Day 57 only for MN) in flavivirus-seronegative participants at baseline (seroresponse is defined as an increase in ZIKV-specific nAb titer [as measured by PRNT or MN] from below the LLOQ to greater than or equal to the LLOQ).
- Increase from baseline of 2-fold or 4-fold in ZIKV-specific nAb titers at Days 8, 29, 36, and 57, as measured by PRNT and MN, in flavivirus-seropositive participants at baseline.

Exploratory Immunogenicity Endpoints

- GMT of ZIKV-specific nAbs at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN.
- GMT of ZIKV-specific nAbs at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seronegative participants at baseline.
- GMT of ZIKV-specific nAbs at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seropositive participants at baseline.
- GMFR of ZIKV-specific nAbs in all participants, in initially flavivirus-seronegative, and in initially flavivirus-seropositive participants at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN.
- Seroconversion from Day 1 (baseline) to Days 85, 196, 364, 532, and 700, as measured by PRNT and MN.
- Seroresponse at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seronegative participants at baseline.
- Increase from baseline of 2-fold or 4-fold in ZIKV-specific nAb titers at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seropositive participants at baseline.
- Proportion of all participants, of baseline flavivirus-seronegative participants, and of baseline flavivirus-seropositive participants with a ZIKV-specific nAb titer equal or greater than a nAb titer defined as a protective level in an animal model, at baseline, and Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by PRNT.
- Proportion of all participants, of baseline flavivirus-seronegative participants, and of baseline flavivirus-seropositive participants with a ZIKV-specific nAb titer equal or greater than a nAb titer defined as a protective level in an animal model, at baseline, and Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by MN.
- GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP.
- GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP, in flavivirus-seronegative participants at baseline.

- GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP, in flavivirus-seropositive participants at baseline.
- Seroconversion from Day 1 (baseline) to Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP.
- Seroresponse at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP in flavivirus-seronegative participants at baseline.
- Increase from baseline of 2-fold or 4-fold in ZIKV-specific nAb titers at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP in flavivirus-seropositive participants at baseline.
- Geometric mean concentration (GMC) of ZIKV-specific serum ligand binding antibodies (bAbs) at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay.
- GMC of ZIKV-specific bAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seronegative participants at baseline.
- GMC of ZIKV-specific bAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532 and 700, as measured by ligand binding assay, in flavivirus-seropositive participants at baseline.
- Seroconversion from Day 1 (baseline) to Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay.
- Seroresponse at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seronegative participants at baseline.
- Increase from baseline 2-fold or 4-fold in bAb concentrations at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seropositive participants at baseline.
- Frequency of ZIKV-specific T cells at Days 1 (baseline), 29, 36, 57, 196, 364, 532, and 700, as measured by intracellular cytokine staining assay and sequencing (CMI subset of baseline flavivirus-seronegative and -seropositive participants).
- Frequency of ZIKV-specific B cells at Days 1 (baseline), 29, 36, 57, 196, 364, 532, and 700, as measured by ELISpot (CMI subset of baseline flavivirus-seronegative and -seropositive participants).
- Additional assays to profile the T- and B-cell responses may also be performed (CMI subset of baseline flavivirus-seronegative and -seropositive participants).
- GMC of nonstructural protein 1 (NS1) -specific serum bAbs at Days 1 (baseline), 85, 196, 364, 532, and 700, as measured by enzyme-linked immunosorbent assay (ELISA).
- Seroconversion (NS1-specific bAbs) from Day 1 (baseline) to Days 85, 196, 364, 532, and 700.

Overall Study Design:	All participants will be evaluated for their eligibility for enrollment in the Vaccination Period and will be followed for approximately 6 months (Day 196) after their last IP injection. All participants in all treatment arms will have the opportunity to continue to be followed as part of an approximately 24-month Extension Period (through Day 700) after their last IP injection. A total of approximately 800 participants will be randomly assigned to receive either CCI µg or CCI µg mRNA-1893 administered as a 2-dose regimen with at least a 28-day interval between vaccinations (Treatment Arm A or Treatment Arm B), or CCI µg mRNA-1893 administered as a 1-dose regimen (Treatment Arm C), or placebo control administered as a 2-dose regimen with at least a 28-day interval between doses (Treatment Arm D) according to a 1:1:1:1 randomization ratio (ie, 200 participants per treatment arm with approximately 100 participants per baseline flavivirus serostatus in each treatment arm). Randomization was stratified by participants' baseline flavivirus serostatus in the original protocol (dated 21 Feb 2021). Under this current protocol amendment, randomization will be stratified only by participants' region (continental United States [US] and Puerto Rico). All treatment arms will be enrolled in parallel. In order to maintain the blinding and to have the same study evaluation time point with both mRNA-1893 dose regimens relative to the last IP injection, participants randomly assigned to Treatment Arm C will be administered placebo at Day 1 and mRNA-1893 at Day 29. Participants will be observed for immediate safety assessment for 30 minutes after IP injection. They will be asked to record solicited local and systemic ARs within 7 days after each administration and unsolicited AEs within 28 days after each administration by completing eDiaries. They will also be asked to report any SAEs, AESIs, or MAAEs from first vaccination until End of Study (up to 24 months after the last IP injection). Blood samples will be collected from all participants for immunogenicity analyses. A subset of participants identified as the "CMI subset", approximately 20 participants per treatment arm per serostatus subgroup (approximately 160 participants in total), will be selected from approximately 4 sites that have experience in human cell collection. Peripheral blood mononuclear cells (PBMCs) will be isolated from blood samples from the CMI subset participants and evaluated for cellular immunity up to Day 196 with an optional participation every 6 months up to Day 700 for the participants included in the Extension Period. All participants will have up to 8 clinic visits (Days 0 [Eligibility Visit], 1 [baseline], 8, 29, 36, 57, 85, and 196) and 3 safety telephone calls (Days 112, 140, and 168). Participants who continue into the Extension Period will have 3 additional clinic visits at Days 364, 532, and 700.

	Participants who withdraw from further IP injection for any reason after their first IP injection but do not withdraw consent will complete all study procedures through the End of Study (EOS) Visit.
Study Safety Oversight:	Study safety will be monitored by an Oversight Safety Team that will include the investigators participating in the study and the protocol team, which will include the contract research organization (CRO) Medical Monitor and the Sponsor Clinical Development Physician and may include additional representatives from the Sponsor Project Team. The CRO Medical Monitor will be responsible for performing a review of the enrollment and study-related safety data with oversight by the Sponsor Clinical Development Physician. During the Vaccination Period, a formal biweekly meeting/teleconference will be scheduled among the CRO Medical Monitor, the Sponsor Clinical Development Physician, and the Lead Investigator (or alternate investigator) to review safety events in a blinded fashion. Once all participants in all treatment arms enter the Follow-Up Period, the interval of these meetings may be extended to monthly. This decision will be confirmed by the protocol team. In addition, an independent Data Safety Monitoring Board (DSMB) will be established for Study mRNA-1893-P201. It will be composed of experts with experience in clinical development and vaccines and with expertise in flaviviruses. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will convene on an approximately quarterly basis until study end. Additionally, the DSMB may convene at any time if there is an ad-hoc safety concern detected by the protocol team. This independent board will be informed of the progress and conduct of the study; their primary responsibility will be to review unblinded study data to evaluate the safety findings. All AEs, SAEs, AESIs and MAAEs will be reviewed by the board, and they will be asked to provide recommendations and guidance as to management of follow-up within the study. In addition, should immunogenicity findings request further opinion, the DSMB would be asked to review unblinded immunogenicity data and provide guidance.
Study Duration:	The planned study duration will be approximately 6 months for all participants. Additionally, all participants will have the opportunity to provide their consent to participate in the Extension Period of up to approximately 24 months (through Day 700) after their last IP injection.
Population:	The study will enroll approximately 800 adult participants aged 18 through 65 years at baseline, including approximately 400 flavivirus-seropositive participants and 400 flavivirus-seronegative participants, who will receive mRNA-1893 or placebo. Flavivirus serology testing (to determine if a participant is flavivirus seronegative or flavivirus seropositive at baseline) is not an enrollment criterion. A dengue rapid point-of-care test initially used to stratify study participants has been discontinued. After this protocol amendment, all participants will be stratified based on

	geographic region, assuming most of the baseline seronegatives will come from the continental US sites and baseline seropositives from Puerto Rico. The confirmation will be based on flavivirus serology testing (dengue immunoglobulin G (IgG) and immunoglobulin M (IgM), West Nile IgG and IgM) performed on a blood sample collected prior to administration of the first vaccination, with a goal of an approximately equal distribution of participants among seronegative and seropositive participants within each treatment group.
Number of Participants:	Approximately 800
Sample Size Determination:	The sample size for this study is not driven by statistical assumptions for formal hypothesis testing. This sample size is regarded as sufficient to provide an understanding of the safety profile of mRNA-1893 and to confirm the dose selection to advance development into future studies. Approximately 800 participants will be randomly assigned in a 1:1:1:1 ratio to the 4 treatment arms. A total of 600 participants will receive mRNA-1893, 200 participants in each dosing arm, with approximately 100 participants in each flavivirus serostatus cohort and dosing arm; approximately 200 participants will receive placebo. A sample size of 200 (or 400) has at least a 95% probability to observe at least 1 participant with an AE at a true 1.49% (or 0.75%) AE rate. For the comparison of immunogenicity, the sample size will provide adequate statistical power (approximately 90%) to detect a large effect size (4-fold or above in ZIKV-specific nAb titers, as measured by PRNT50 at Day 57) under reasonable assumptions.
Inclusion Criteria:	Participants are eligible to be included in the study only if all the following criteria apply: 1. Male or female participant aged 18 through 65 years at the time of consent. 2. Understands and agrees to comply with the study procedures and provides written informed consent. 3. According to investigator assessment, is in good general health and can comply with study procedures. 4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to the eligibility evaluation without an alternative medical cause). The follicle-stimulating hormone level may be measured at the discretion of the investigator to confirm postmenopausal status. 5. Female participants of childbearing potential may be enrolled in the study if the participant: 1) has a negative pregnancy test at the Eligibility Visit and on the day of the first IP injection, 2) has practiced adequate contraception or has abstained from all

	activities that could result in pregnancy for at least 28 days prior to the first IP injection, 3) has agreed to continue adequate contraception through 3 months following the last IP injection, and 4) is not currently breastfeeding. Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration-approved contraceptive method in accordance with the product label. Examples are as follows: • Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide. • Intrauterine device. • Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or intramuscular (IM) route. • Sterilization of a female participant's monogamous male partner prior to entry into the study. Note: periodic abstinence (eg, calendar ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Exclusion Criteria:	Participants are excluded from the study if any of the following criteria apply: 1. Is acutely ill or febrile (temperature ≥ 38.0°C/100.4°F) on the day of the first or second vaccination. Participants meeting either of these criteria may be rescheduled for enrollment/randomization if the event resolves within the vaccination window. 2. Had prior administration of a ZIKV vaccine candidate during a clinical study investigation. 3. Had prior administration of a marketed dengue vaccine or dengue vaccine candidate under clinical study investigation. 4. Has a body mass index (BMI) from ≤ 18 or ≥ 35 kg/m^2. 5. History of myocarditis, pericarditis, or myopericarditis. 6. History of a diagnosis or condition that, in the judgement of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. "Clinically unstable" is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to screening and includes ongoing work-up of an undiagnosed illness that could lead to a new diagnosis or condition. 7. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that in the opinion of the investigator, might pose a risk due to participation in the study or could interfere with the interpretation of study results. 8. Has a known or suspected autoimmune disease, including hypothyroidism in relation to autoimmune thyroiditis.

9. Has a history of progressive or severe neurologic disorder or a history of neuroinflammatory disease such as Guillain-Barré Syndrome.
10. Has a history of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine, including an mRNA vaccine or any components of an mRNA vaccine.
11. Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
12. Has been diagnosed with malignancy within the previous 10 years (excluding nonmelanoma skin cancer).
13. Has received or plans to receive a nonstudy vaccine (including authorized or approved vaccines for the prevention of coronavirus disease 2019 [COVID-19]) ≤ 28 days prior to the first IP injection or within 28 days prior to or after any IP injection. Licensed influenza vaccine received within 14 days prior to the first IP injection or plans to receive a licensed influenza vaccine 14 days prior to through 14 days following each IP injection are not exclusionary.
14. Has a known or suspected impairment or alteration of immune function including the following:
    a. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks or ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
    b. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks or ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1.
    c. Receipt of immunosuppressive therapy within 3 months prior to Day 1 or planned during the 7-month period following study enrollment.
    d. Receipt of immunostimulants within 60 days prior to Day 1.
    e. Receipt of parenteral, epidural, or intra-articular immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to Day 1 or planned during the 7-month period following study enrollment.
    f. HIV infection or HIV-related disease.
    g. Genetic immunodeficiency.
15. Has received systemic immunoglobulins or blood products within 3 months prior to the day of enrollment or planned during the 7-month-period following study enrollment.
16. Has donated ≥ 450 mL of blood products within 28 days of the Day 1 Visit.
17. Has participated in an interventional clinical study within 28 days prior to the day of enrollment or plans to do so while enrolled in this study.

	18. Is an immediate family member or household member of study personnel.
Investigational Products, Dosage, and Route of Administration:	mRNA-1893 consists of a messenger RNA sequence that encodes the full pre-membrane and envelope structural polyprotein of ZIKV in a liposomal formulation. The lipid nanoparticle formulation includes 4 lipid excipients (1 proprietary and 3 commercially available). mRNA-1893 will be provided as a 0.20 mg/mL dispersion in 2R glass vials labeled as required per country requirement. The vaccine will be diluted with 0.9% sodium chloride solution for injection (United States Pharmacopeia [USP] or British Pharmacopeia [BP]) to a concentration for delivery of the specified dose level in a volume of 0.5 mL. The IP will be administered as an IM injection into the deltoid muscle on a 2-dose dose schedule on Days 1 and 29, with at least a 28-day interval between doses. Each dose will have a volume of 0.5 mL and will contain either mRNA-1893 CCI µg or mRNA-1893 CCI µg, or placebo. Preferably, the first dose should be injected into the nondominant arm. The second dose should be injected into the same arm as the first dose. The placebo is 0.9% sodium chloride solution for injection, USP or BP. Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform IP accountability, IP preparation, and administration.
Assessments and Procedures:	**Safety Assessments:** Safety assessments will include monitoring and recording of the following for each participant: • Solicited local and systemic ARs that occur during the 7 days following each IP injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using electronic diaries (eDiaries). • Unsolicited AEs observed or reported during the 28 days following each IP injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs. • AEs leading to discontinuation from IP and/or study participation throughout the entire study duration (up to Day 700). • MAAEs from Day 1 throughout the entire study duration (up to Day 700). • SAEs and AESIs from Day 1 throughout the entire study duration (up to Day 700). • Physical examination findings. • Vital sign measurements.

Immunogenicity Assessments:

Immunogenicity assessments will include the following:

- Serum ZIKV-specific nAb titers, as measured by PRNT assay, MN assay, and RVP assay.
- Serum ZIKV-specific bAb concentrations, as measured by ligand binding assay.
- Frequency of ZIKV-specific T cells, as measured by ICS assay and sequencing and frequency of ZIKV-specific B cells, as measured by ELISpot. Other techniques that may be relevant to assess the profile characteristics of the ZIKV-specific T- and B-cell responses may be included.

Efficacy Assessments:

- Asymptomatic flavivirus infections, assessed through quantification of NS1 bAbs, as measured by ELISA.
- Symptomatic flavivirus infections, assessed by specific serology (IgM antibody capture ELISA and virus neutralization assay) and RT-PCR.

Statistical Plan:

Populations for Analyses:

- The Randomized Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. Participants will be included in the treatment arm to which they are randomized.
- The Solicited Safety Set consists of all participants who are randomly assigned and received any IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the treatment arm corresponding to the IP they actually received.
- The Safety Set consists of all participants who are randomly assigned and received any IP. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the treatment arm corresponding to the IP they actually received for the analysis of safety data using the Safety Set.
- The Full Analysis Set (FAS) consists of all participants who are randomly assigned and a) received any IP, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least 1 post-IP injection assessment for those analysis endpoints as specified in b). Participants will be included in the treatment arm to which they are randomly assigned.
- The Per-Protocol (PP) Set consists of all FAS participants who a) comply with the vaccination schedule, b) comply with the timings of immunogenicity blood sampling to have post-IP injection results available for at least 1 assay component corresponding to the immunogenicity analysis objective, and c) have no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective. The PP set will serve as the primary population for the

analysis of immunogenicity data in this study. Participants will be included in the treatment arm to which they are randomly assigned.

Safety Analyses:

Safety analyses will include solicited ARs (local and systemic), unsolicited AEs, SAEs, AESIs, MAAEs, and AEs leading to vaccine/study withdrawal, and vital sign measurements.

Solicited ARs, unsolicited AEs, and vital sign measurements will be graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

All safety analyses will be based on the Safety Set, except analyses of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment arm overall (regardless of serostatus) and by baseline flavivirus status assessed by dengue and West Nile specific serologies, and vaccination (first, second), unless otherwise specified.

Solicited local and systemic ARs during the 7-day follow-up period after each IP injection will be tabulated by number and percentage of participants reporting ≥ 1 event. The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each IP injection will be provided with a 2-sided 95% exact CI using the Clopper-Pearson method.

Unsolicited AEs will be coded according to the Medical Dictionary for Regulatory Activities (Dictionary for Adverse Reaction Terminology version). Unsolicited AEs, treatment-related AEs, SAEs, AESIs, MAAEs, and AEs leading to discontinuation from IP or participation in the study, severe AEs, and deaths will be reported by number and percentage of participants reporting ≥ 1 event, and number of events.

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by treatment arm overall (regardless of baseline serostatus) and by baseline flavivirus status assessed by dengue and West Nile specific serologies and treatment arm by descriptive statistics (mean, median, minimum, maximum, and standard deviation for continuous variable, and number and percentage for categorical variables).

Further details will be described in the statistical analysis plan (SAP).

Immunogenicity Analyses:

Immunogenicity analyses will be conducted on the PP set, reported by treatment arm overall and by baseline flavivirus status assessed by dengue and West Nile specific serologies, as applicable. If the number of participants in the FAS and PP set differ by more than 10%, supportive immunogenicity analyses may be conducted on the FAS.

For the primary and secondary immunogenicity endpoints, descriptive summary statistics of antibody-mediated immunogenicity at each time point will include GMT (for nAbs) median, minimum, maximum, 95% CI, and GMFR of post-baseline/baseline nAb titers.

For GMT calculations, antibody titers reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with seroconversion will be provided with 2-sided 95% CI using Clopper-Pearson method by treatment arm overall and also by the baseline flavivirus serostatus.

The number and percentage of participants with seroresponse will be provided with 2-sided 95% CI using Clopper-Pearson method by treatment arm overall and in baseline flavivirus-seronegative participants.

The number and percentage of participants with ≥ 2- or ≥ 4-fold rise in ZIKV-specific nAb titers will be provided with 2-sided 95% CI using Clopper-Pearson at each post-baseline timepoint.

Further details will be described in the SAP.

Study Planned Analyses:

The following analyses will be conducted on cleaned data:

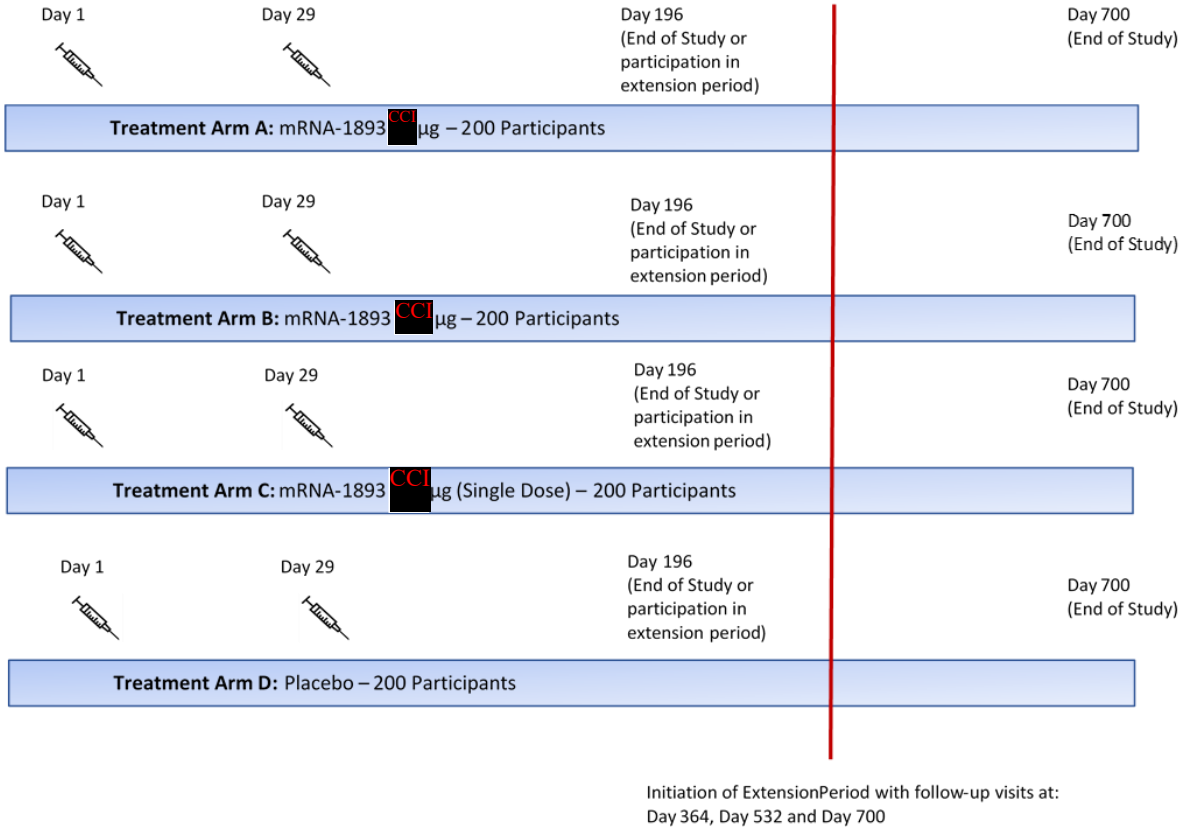
1. An interim analysis (IA) of safety and immunogenicity data will be performed after all participants have completed Day 57 (28 days after the last IP injection). The Day 57 IA will be performed by a separate team of unblinded programmers and statisticians. Pre-identified Sponsor team members will be unblinded to review treatment level results, as defined in the study Data Blinding Plan. The unblinded statistics team will not be involved in either study design or the regular study conduct. The participants and study sites will remain blinded until the conclusion of the study. The IA will serve as the basis for the progression to the ZIKV Phase 3 studies.
2. The final clinical study report (CSR) will include full unblinded analyses of all safety and immunogenicity with individual unblinded listings through Day 196 (all data through approximately 6 months after the last IP injection).
3. An addendum to the CSR will include the safety and immunogenicity data from Month 8 until EOS for all participants enrolled in the Extension Period.

More details can be found in the SAP.

In addition, unblinded data presentation or analysis for DSMB review will be handled by the unblinded team of statisticians and programmers, who are not involved in study design. More details regarding DSMB analysis can be found in the DSMB Charter.

1.2. Schema

Figure 1: Study Schema



Abbreviations: mRNA = messenger RNA.

Note: Participants randomly assigned to Treatment Arm C will be administered placebo at Day 1 and mRNA-1893 CCI µg at Day 29.

1.3. Schedule of Assessments

The Schedules of Assessments for the Vaccination Period and the Extension Period are presented in Table 1 and Table 2, respectively.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Day 0, Day 1, and Day 29 Visits, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a home visit to the participant is possible (with the exception of Day 0, Day 1, and Day 29 Visits), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls scheduled on Days 112 through 168 (Table 1).

Table 1: Schedule of Assessments for the Vaccination Period and for the Follow-Up Period (Approximately 6 Months)

Procedure	**Eligibility**	**Vaccination Period**						**Follow-Up Period**		**Unscheduled**
Study Day	**D0[1] (Eligibility)**	**D1[1] (Baseline)**	**D8**	**D29**	**D36**	**D57**	**D85**	**D112, D140, D168**	**D196**	
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-9**	**10 and EOS[2]**	**Unscheduled**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Window Allowance (Days)	**-8**		**+3**	**-3/+7**	**+3**	**-3/+7**	**-3/+7**	**± 15**	**± 15**	
Informed consent, inclusion and exclusion criteria, demography, prior and concomitant medications, and medical history	X									
Physical examination and vital sign measurements[3]	X	X	(X)	X	(X)	X	(X)		(X)	(X)
Blood sample for baseline flavivirus serostatus assessments[4, 5]		X								

Procedure	**Eligibility**	**Vaccination Period**						**Follow-Up Period**		**Unscheduled**
Study Day	**D0[1] (Eligibility)**	**D1[1] (Baseline)**	**D8**	**D29**	**D36**	**D57**	**D85**	**D112, D140, D168**	**D196**	
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-9**	**10 and EOS[2]**	**Unscheduled**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Window Allowance (Days)	**-8**		**+3**	**-3/+7**	**+3**	**-3/+7**	**-3/+7**	**± 15**	**± 15**	
Blood sample for antibody-mediated immunogenicity[6]		X	X	X	X	X[7]	X		X	
PBMC collection for cellular immunity (subset of participants from approximately 4 selected sites)		X		X	X	X			X	
Pregnancy test[8]	X	X		X						
Randomization		X								
IP injection (including 30-minute safety observation period after IP injection)[9]		X		X						
Participant eDiary recording of solicited ARs (7 days)		X (Days 1-7)		X (Days 29-35)						
Participant eDiary recording of unresolved solicited ARs (up to 28 days)		X (Days 1-29 and Days 29-57)								
Review of eDiary			X		X					
Follow-up safety telephone call[10]								X		
Recording of MAAEs		X	X	X	X	X	X	X	X	X
Recording of SAEs and AESIs		X	X	X	X	X	X	X	X	X

Procedure	Eligibility	Vaccination Period						Follow-Up Period		Unscheduled
Study Day	**D0[1] (Eligibility)**	**D1[1] (Baseline)**	**D8**	**D29**	**D36**	**D57**	**D85**	**D112, D140, D168**	**D196**	
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-9**	**10 and EOS[2]**	**Unscheduled**
Type of Visit	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**SC**	**C**	**C**
Window Allowance (Days)	**-8**		**+3**	**-3/+7**	**+3**	**-3/+7**	**-3/+7**	**± 15**	**± 15**	
Recording of concomitant medications and nonstudy vaccinations		X	X	X	X	X	X	X	X	X
Blood sample for asymptomatic flavivirus infection detection[11]							X		X	
Blood sample for symptomatic flavivirus infection detection[11]										X
Informed consent to participate in the Extension Period									X[12]	

Abbreviations: AE = adverse event; AESIs = adverse events of special interest; AR = adverse reaction; C = clinic visit; CMI = cell-mediated immunity; D = day; eDiary = electronic diary; EOS = End of Study; IP = investigational product; MAAE = medically attended adverse event; mRNA = messenger RNA; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SC = safety (phone) call; US = United States.

1 The Eligibility (Day 0) and Baseline (Day 1) Visits may be combined on the same day.

2 This visit will be the EOS for all enrolled participants who do not elect to continue into the Extension Period. For participants enrolled in Treatment Arm A (2-dose regimen with CCI µg mRNA-1893), Treatment Arm B (2-dose regimen with CCI µg mRNA-1893), Treatment Arm C (1-dose regimen with CCI µg mRNA-1893), and Treatment Arm D (placebo) who elect to take part in the Extension Period, return visits will occur approximately every 6 months after the last IP injection (Table 2).

3 A full physical examination, including weight, and vital sign measurements will be performed at the eligibility evaluation and Days 1, 29, and 57. Height measurements will only be collected at Day 1. Symptom-directed physical examinations may be performed at other scheduled timepoints (X) at the discretion of the investigator. Vital sign measurements (body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) will be collected before study procedures and at least 30 minutes after IP injection, prior to discharge of the participant from the study site. Any clinically significant finding identified during a study visit should be reported as an MAAE. Body mass index will be calculated (Section 8.5.3) during the eligibility evaluation.

4 Flavivirus serology testing is to determine if a participant is flavivirus seronegative or flavivirus seropositive at baseline. This is not an enrollment criterion. However, this flavivirus serology testing needs to be performed on a blood sample collected prior to administration of the first vaccination to confirm that the study distribution among subgroups is respected.

5 Follicle-stimulating hormone level may be measured to confirm menopausal status at the discretion of the investigator.

[6] Blood samples must be collected before injection on vaccination days (Days 1 and 29).

[7] At Visit 5 (Day 57), an additional blood sample (60 mL) will be collected for exploratory research (Table 9 and Section 11.1.10) from participants enrolled at 1 US site. This site will be different from those sites selected for cellular immunity.

[8] Pregnancy testing at the Eligibility Visit (Day 0) and before each IP injection (or at any time at the discretion of the investigator) will be a point-of-care urine test.

[9] Participants will be administered the IP (mRNA-1893 or placebo) according to the randomization. Participant will remain at the study site for safety monitoring for at least 30 minutes after IP injection.

[10] Trained study personnel will call all participants to collect information relating to any MAAEs, SAEs, AESIs, AEs leading to study discontinuation, concomitant medications associated with those events, and any nonstudy vaccinations.

[11] Blood samples collected from all participants at Visit 6 (Day 85) and Visit 10 (Day 196) will be used for detection of asymptomatic flavivirus infections. In case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed), an additional blood sample will be collected to confirm the diagnosis via specific serology and RT-PCR, and clinical information will be carefully collected to evaluate the severity of the clinical case. Those symptoms are not specific; however, an association of acute fever onset with maculopapular rash, arthralgia, and conjunctivitis during the seasonal circulation of mosquitos must trigger samplings. Also, special attention will be paid to the reporting of neurological signs or symptoms evoking Guillain-Barré syndrome.

[12] At Visit 10 (Day 196), all participants will have the opportunity to provide their consent to participate in the Extension Period (Table 2).

Table 2: Schedule of Assessments for the Extension Period

Procedure	Extension Period			
Study Day	**D364**	**D532**	**D700**	
Visit Number	**11**	**12**	**13 and EOS**	**Unscheduled**
Type of Visit	**C**	**C**	**C**	**C**
Window Allowance (Days)	**± 15**	**± 15**	**± 30**	
Physical examination (including weight) and vital sign measurements)[1]	(X)	(X)	(X)	(X)
Blood sample for antibody-mediated immunogenicity	X	X	X	
PBMC collection for cellular immunity (CMI subset participants selected during the Vaccination Period)	X	X	X	
Blood sample for asymptomatic flavivirus infection detection[2]	X	X	X	
Blood sample for symptomatic flavivirus infection detection[2]				X
Recording of MAAEs	X	X	X	X
Recording of SAEs and AESIs	X	X	X	X
Recording of concomitant medications and nonstudy vaccinations	X	X	X	X
Study completion			X	

Abbreviations: AESIs = adverse events of special interest; C = clinic visit; CMI = cell-mediated immunity; D = day; EOS = End of Study; MAAE = medically attended adverse event; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event.

[1] Symptom-directed physical examinations might be performed at the scheduled timepoints (X) at the discretion of the investigator. Vital sign measurements (body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) will be collected before study procedures. Any clinically significant finding identified during a study visit should be reported as an MAAE.

[2] Blood samples collected from all participants at Visits 11, 12, and EOS (Days 364, 532, and 700, respectively) will be used for detection of asymptomatic flavivirus infections. In case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed), an additional blood sample will be taken to confirm the diagnosis via specific serology and RT-PCR, and clinical information will be carefully collected to evaluate the severity of the clinical case. Special attention will be paid to collect signs or symptoms possibly related to Guillain-Barré syndrome.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
bAb	Binding antibody
BMI	Body mass index
BP	British Pharmacopeia
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CMI	Cell-mediated immunity
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunosorbent spot
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

Abbreviation or Specialist Term	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
hMPV	Human metapneumovirus
HRT	Hormonal replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular(ly)
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LOD	Limit of detection
LTFU	Lost to follow-up
MAAE	Medically attended adverse event
MN	Microneutralization
mRNA	Messenger RNA
nAb	Neutralizing antibody

Abbreviation or Specialist Term	Definition
NS1	Nonstructural protein 1
OST	Oversight safety team
PBMC	Peripheral blood mononuclear cell
PIV3	Parainfluenza virus type 3
PP	Per-protocol
prME	Pre-membrane and envelope
PRNT	Plaque reduction neutralization test
QA	Quality assurance
RT-PCR	Reverse transcription polymerase chain reaction
RVP	Reporter virus particle
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCR	Seroconversion rate
SM-102	Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6(undecyloxy)hexyl)amino)octanoate
SOA	Schedule of Assessments
ULOQ	Upper limit of quantification
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization
ZIKV	Zika virus
ZPIV	Zika virus purified inactivated vaccine

2. INTRODUCTION

2.1. Study Rationale

The purpose of this Phase 2 randomized, observer-blind, placebo-controlled, dose confirmation study is to evaluate the safety, tolerability, and immunogenicity of messenger RNA (mRNA)-1893 in adults aged 18 through 65 years living in endemic and non-endemic flavivirus areas.

2.2. Background and Overview

Zika virus (ZIKV) is a mosquito-borne and sexually transmitted single-stranded RNA virus of the Flaviviridae family, which includes yellow fever, dengue, West Nile, and Japanese encephalitis viruses. First discovered in 1947, ZIKV was recognized sporadically as a cause of mild, self-limited febrile illness in Africa and Southeast Asia. In 2007, an outbreak occurred on the North Pacific island of Yap, subsequently spreading through Oceana to re-emerge in 2013 and 2014 in an outbreak in French Polynesia before spreading to the Americas in 2015 (Duffy et al 2009; Derraik and Slaney 2015; Campos et al 2015). The outbreaks from 2015 onward have been of major public health concern due to their associated clinical complications such as Guillain-Barré syndrome in adults and a wide range of birth defects, including microcephaly, intrauterine growth restriction, and spontaneous abortion (Brasil et al 2016; Cao-Lormeau et al 2016).

The devastating consequences of ZIKV infection led the World Health Organization (WHO) to declare a public health emergency of international concern on 01 Feb 2016 (Heymann et al 2016) and to call on the global research and development communities to prioritize the development of preventive and therapeutic solutions (WHO 2016a). Although the WHO declared an end to its global health emergency over the spread of ZIKV in November 2016, the long-term need for a ZIKV vaccine continues (WHO 2019) as a priority need under the Blueprint plan of action (WHO 2016b).

Currently there is no approved vaccine to protect against ZIKV disease.

To address the public health need, the Sponsor is developing mRNA-1893, a prophylactic vaccine against ZIKV. mRNA-1893 is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine directed against the pre-membrane and envelope (prME) structural proteins of ZIKV. Following uptake of the LNP by the cell, the mRNA is translated and processed within the cytosol by the host cell, stimulating 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. Details on the mechanism of action and a summary of nonclinical studies of mRNA-1893 can be found in Section 2.2.1.

mRNA-1893 was tested in a Phase 1 clinical study (Study mRNA-1893-P101; NCT04064905) evaluating the safety and immunogenicity of 4 dose levels (CCI [redacted] µg) in a liquid formulation in approximately 100 healthy flavivirus-seronegative adults and 20 healthy flavivirus-seropositive adults. The study was performed at 4 sites (3 in the continental United States [US] and 1 in Puerto Rico). Additional details on this clinical study and other clinical studies across the Sponsor's infectious disease vaccine platform with mRNA vaccines using the same novel heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6(undecyloxy)hexyl)amino)octanoate (SM-102)-containing lipid formulation are described in Section 2.2.2.

The Phase 2 Study mRNA-1893-P201 is intended to confirm the safety and immunogenicity trends observed during the Phase 1 study. Two dose levels and 2 dosing schedules of mRNA-1893 will be tested in this Phase 2 study for comparison to a placebo control. The 2 dose levels, CCI µg and CCI µg, will be compared for a 2-dose schedule, with doses 28 days apart. One single dose of the CCI µg-dose level will also be tested to explore its safety profile and characterize the intensity and persistence of the ZIKV-specific immune response.

The Phase 2 primary study objectives will be the Day 57 assessment for humoral immunogenicity and safety with a planned study end date approximately 6 months after the last investigational product (IP) injection (Day 196) for all treatment arms. However, the study will be extended to approximately 24 months after the last IP injection for all participants who elect to enroll to assess the long-term safety of mRNA-1893, to assess the persistence of the ZIKV-specific immune response, and to capture the eventual occurrence of flavivirus infections.

The Phase 2 study has already started to enroll participants; however, goals and treatment arms will not change with the current protocol amendment.

The Phase 2 study will be conducted under US Investigational New Drug application in accordance with the protocol, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

2.2.1. Nonclinical Studies

In support of development of mRNA-1893 for prophylaxis against ZIKV infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with mRNA-1893 or similar mRNA-based vaccines formulated in SM-102-containing LNPs.

In a non-Good Laboratory Practice (GLP) in vivo dose-range finding study, immunogenicity (binding antibody [bAb] and neutralizing antibody [nAb] titers) to the mRNA-1893 encoded protein was evaluated in female C57BL/6 mice at 4 doses CCI [redacted] µg) following intramuscular (IM) injection on Days 1 and 29. mRNA-1893 generated strong nAb and bAb titers

at multiple doses. Mice dosed with CCI µg mRNA-1893 generated higher nAb and bAb titers than mice dosed with CCI µg mRNA-1893. Mice dosed with CCI µg mRNA-1893 generated higher bAb titers compared with mice dosed with CCI µg mRNA-1893.

The immunogenicity and efficacy of mRNA-1893 were evaluated in a non-GLP study in the rhesus macaque ZIKV infection model. A total of 40 monkeys were randomly assigned to 1 of 7 groups to receive mRNA-1893 CCI µg), ZIKV purified inactivated vaccine (ZPIV [400 antigenic units]), a formalin-inactivated ZIKV strain PRVABC59 shown to be immunogenic in human, or buffer control. Dose administration occurred via IM injection on Day 0 and Day 28. Following blood collections on Day 56, animals were challenged by subcutaneous injection with a target dose of 1×10^5 plaque-forming units of ZIKV strain PRVABC59. Overall, administration of mRNA-1893 by IM injection (2 doses) was clinically well tolerated, with no mRNA-1893-related mortality, clinical observations, or changes in body weight. Animals in the buffer control group developed viremia that persisted for 3 to 7 days, whereas mRNA-1893- and ZPIV-treated animals were either negative for ZIKV RNA at all time points evaluated or had sporadic instances of low levels of ZIKV RNA at a single time point after ZIKV challenge. Detection of ZIKV RNA was inversely related to detection of ZIKV nAbs prior to ZIKV challenge. mRNA-1893– and/or ZPIV-treated animals had detectable nAb titers in the ZIKV microneutralization (MN) assay at Days 28 and 56 as well as at the End of Study (EOS) (Day 77, 21 days after ZIKV challenge), whereas animals in the buffer control group did not have ZIKV-neutralizing titers until after ZIKV challenge on Day 77.

Overall, these results demonstrate that mRNA-1893 generates strong immunogenic response in mice and non-human primates and prevents viremia, with either no or low levels of ZIKV RNA upon challenge in the rhesus macaque ZIKV infection model.

To evaluate the generalized tissue distribution and tissue half-life of mRNA-1893, the biodistribution of mRNA-1647, a similar mRNA-based vaccine formulated in SM-102-containing LNPs, was evaluated in male rats. mRNA-1647 is a novel mRNA-based cytomegalovirus (CMV) vaccine formulated in a mixture of the same 4 lipids as mRNA-1893. The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics. Therefore, mRNAs that are within an LNP of the same composition (eg, mRNA-1893 and mRNA-1647) are expected to distribute similarly. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than the vaccination site, lymph nodes, and spleen.

The safety and tolerability of 3 dose levels of mRNA-1893 administered by IM injection were evaluated in a GLP-compliant, repeat dose (1 month; 3 doses) toxicity study in Sprague Dawley rats followed by a 2-week recovery period. Animals were administered mRNA-1893 at doses of

CCI µg/dose or phosphate buffered saline via IM injection on Days 1, 15, and 29. The results of this study indicated that administration of mRNA-1893 was clinically tolerated in rats up to CCI µg/dose with no mortality or changes in body weight or food consumption. Starting at CCI µg/dose, dose-dependent clinical signs (swelling/firmness/redness/scabs) at the injection site, changes in clinical pathology parameters and cytokines concentrations, and an increase in body temperature were observed and were consistent with an inflammatory reaction. Dose-dependent effects were observed at the vaccination site, spleen, liver, and seminal vesicle of animals given mRNA-1893. Additional microscopic findings in the iliac, inguinal, and popliteal lymph nodes or their perinodal tissue; perineural tissue of the sciatic nerve; spleen (extramedullary hematopoiesis); and bone marrow of animals given mRNA-1893 were considered to be an extension, a secondary response, or a reactive response to the vaccination site inflammation. At the end of the 2-week recovery period, all changes were partially or fully recovered.

In GLP-compliant studies, SM-102, the novel lipid component of the LNP formulation, was not genotoxic when tested in a bacterial reverse mutation (Ames) test or an in vitro micronucleus test. An in vivo micronucleus study in Sprague Dawley rats showed that a similar mRNA-based vaccine formulated in SM-102 containing LNPs (mRNA-1706, which encodes the ZIKV prME polypeptide [different from the sequence encoded in mRNA-1893]), induced statistically significant increases in micronucleated immature erythrocytes in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity. These observations indicate that the risk to humans after IM administration is low due to minimal systemic exposure.

A detailed review of nonclinical experience with mRNA-1893 is provided in the Investigator's Brochure (IB).

2.2.2. Clinical Studies

mRNA-1893 was tested in a Phase 1 clinical study (Study mRNA-1893-P101; NCT04064905) evaluating the safety and immunogenicity of 4 dose levels CCI µg) in a liquid formulation in approximately a total of 120 participants aged 18 through 49 years (CCI per dose level with 25 baseline flavivirus-seronegative and 5 flavivirus-seropositive participants). The study was performed at 4 sites (3 in the continental US and 1 in Puerto Rico). Group unblinding interim analyses performed at Day 57 (ie, 28 days after the second vaccine administration of the CCI µg dose levels) showed a safety profile compatible with a large use of the vaccine candidate and a production of ZIKV-specific nAbs, as measured by plaque reduction neutralization test (PRNT), at a seroconversion rate (SCR) of 86.4% (65.1% - 97.1%) at CCI µg dose level, 95.5% (77.2% - 99.9%) at CCI µg dose level, 100% (85.8% - 100%) at CCI µg dose

level, and 95.7% (78.1% - 99.9%) at CCI µg dose level 28 days after the last vaccine administration. Clinical study report (CSR) writing corresponding to the safety and immunogenicity evaluations performed at Month 6 and Month 13 is under preparation.

The Sponsor has demonstrated several mRNA vaccines to confer protection against a variety of pathogens in addition to Zika virus, including SARS-CoV-2, influenza virus, and chikungunya virus, in a variety of animal species such as mice, rats, cotton rats, ferrets, and non-human primates. As of February 2021, mRNA vaccines with SM-102-containing lipid formulations are currently being evaluated for infectious disease indications including: prophylactic protection against coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus (NCT04470427, NCT04649151, NCT04405076, NCT04283461), human CMV (NCT03382405, NCT04232280), human metapneumovirus/parainfluenza virus Type 3 (hMPV/PIV3; NCT04144348, NCT03392389), respiratory syncytial virus (RSV; NCT04528719), influenza virus (NCT04956575), and Zika virus (NCT04064905) infections. The Sponsor's COVID-19 vaccine received authorization in the US for emergency use to prevent COVID-19 infections in adults on 18 Dec 2020.

A detailed review of clinical experience with LNPs containing SM-102 (mRNA vaccines and placebo) is provided in the IB.

2.3. Benefit/Risk Assessment

Approximately 600 participants will be exposed to mRNA-1893 in this study; approximately 200 participants will receive placebo.

A summary of the potential risks and benefits of mRNA-1893 is provided in the current IB.

2.3.1. Known Potential Benefits

Participants who receive mRNA-1893 may or may not directly benefit from vaccination as the protective efficacy of mRNA-1893 has yet to be established.

Participants can obtain medical advice about their general health status through the medical evaluations/assessments associated with this study.

Participants will be contributing to the process of developing a new potentially prophylactic measure against ZIKV in an area of unmet medical need, should ZIKV epidemics re-emerge.

2.3.2. Anticipated Risks

As with all injectable vaccines, immediate systemic allergic reactions, including anaphylaxis, to vaccination can occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein

(Zent et al 2002). As a precautionary measure, all participants will remain under observation at the study site for safety monitoring for at least 30 minutes after IP injection. Vasovagal syncope (fainting) can occur before or after any IP injection, is usually triggered by the pain or anxiety caused by the injection, and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting. Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling/induration (hardness) at the injection site. Most systemic adverse events (AEs) observed after IP injection do not exceed mild to moderate severity and are of short duration.

In Study mRNA-1893-P101 that tested dose levels from CCI to CCI µg, interim safety analyses after 28 days after the last vaccination have been performed. All dose levels were generally well tolerated. However, there was a trend towards more observations of local erythema and swelling/induration at the injection site with higher dose levels and this was evident at the CCI µg dose level, in particular after the second vaccine administration. More solicited systemic ARs were noted at the CCI µg dose level in terms of myalgia, fatigue, headache, chills, fever, and nausea with higher grade intensity. With the acknowledgment that the sample size of seropositive participants was very limited, the baseline flavivirus positive serostatus did not seem to negatively affect the safety profile. No serious adverse event (SAE) and no AEs of special interest related to mRNA-1893 were reported at any dose levels.

Regarding the CCI µg and CCI µg dose levels tested in the mRNA-1893-P101 study, ie, the same dose levels planned to be tested in the Phase 2 study, the most commonly reported solicited systemic adverse reactions (ARs) were: respectively for CCI µg and CCI µg, after the first vaccine administration, headache (21.7% and 12.5%), fatigue (21.7% and 12.5%), myalgia (13% and 4.2%), and nausea (8.7% and 12.5%); and after the second administration, fatigue (45.5% and 41.7%), headache (36.4% and 37.5%), chills (22.7% and 45.8%), myalgia (18.2% and 41.7%), and arthralgia (18.2% and 37.5%). Fever was reported in 4.2% of the participants at the CCI µg dose level after the first vaccine administration corresponding to a Grade 1 intensity in 1 participant, and in 29.2% of participants (7 cases) after the second vaccine administration; among those 7 cases, 2 were of Grade 3 intensity. With the CCI µg dose level, no participant reported fever after the first vaccine administration and 12.6% (3 cases) reported fever of mild or moderate intensity after the second vaccine administration; no fever of Grade 3 was observed. As the dose levels selected for Study mRNA-1893-P201 have been already tested with the same liquid formulation as those used in mRNA-1893-P101, a similar safety profile as the one observed in the Phase 1 study is anticipated.

Laboratory abnormalities (including increases in liver enzymes and in coagulation parameters) following vaccine administrations were observed in clinical studies performed by the Sponsor with mRNA-based vaccine candidates. These abnormalities were without clinical symptoms or signs associated and returned toward baseline (Day 1) values over time; the clinical significance of these observations is unknown. In Study mRNA-1893-P101, inclusion criteria required that all participants had Grade 0 laboratory test results at enrollment. Post-vaccination laboratory abnormalities were infrequent, mostly Grade 1 or Grade 2, except 1 case of Grade 4 prothrombin test increase at Day 29 at the [redacted] µg dose level, not related to the vaccination, and further attributed to a laboratory technical issue. None of those laboratory abnormalities were considered clinically relevant. Further details are provided in the current IB.

There is a theoretical risk that active vaccination to prevent novel viral infection may cause a paradoxical increase in the risk of disease. This possibility is based on the rare phenomenon of vaccine-associated disease enhancement, which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with respiratory syncytial virus (Chin et al 1969) or measles (Fulginiti et al 1967). Antibody disease enhancement has also been proposed as a possible explanation for the cases of more serious disease associated with dengue vaccination (Thomas and Yoon 2019; WHO 2018); this phenomenon was already known in cases of a dengue reinfection caused by a heterologous serotype. It is not known if mRNA-1893 will increase the risk of ZIKV-enhanced disease and also the risk of dengue-virus–enhanced disease because of the close relationship between dengue virus and ZIKV (flavivirus family, geographic location, cross-reactivity). To monitor this risk, the Sponsor will perform a careful safety follow-up throughout the entire study duration by establishing an Oversight Safety Team (OST) and an independent Data Safety Monitoring Board (DSMB). The OST will perform a biweekly review of safety events in a blinded fashion. In addition, the DSMB will convene on an approximately quarterly basis until study end and at any time if there is an ad-hoc safety concern detected by the OST. The DSMB will review unblinded study data to evaluate the safety findings. All AEs, SAEs, and medically attended AEs (MAAEs) will be reviewed in terms of frequency and severity by the board and they will be asked to provide recommendations and guidance as to management of safety follow-up within the study (Section 11.1.1)

There have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. The majority of the cases have been reported in young males shortly after the second dose of the vaccine. The risk is highest in males under the age of 40 years, specifically males between 12 through 17 years. Symptoms include chest pain, shortness of breath, or palpitations. Study participants should seek medical attention and also notify study site staff if

any of these symptoms occur following vaccination. While some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. It is not known whether the risk of myocarditis or pericarditis is increased following additional doses of the vaccine. Investigators and study participants should be alert to the signs and symptoms of myocarditis and pericarditis (Gargano et al 2021).

2.3.3. Overall Benefit/Risk Conclusion

Appropriate eligibility criteria, as well as clearly defined study procedures, are included in this protocol. The risk to participants in this study may be minimized by compliance with the eligibility criteria and study procedures.

All safety findings will be closely monitored biweekly by the OST and reviewed by the independent DSMB during periodic meetings to evaluate the safety and treatment status of all participants. The composition, roles, responsibilities, and governance of the OST and DSMB will be described in separate charters.

Considering the safety profile observed in Study mRNA-1893-P101 and the measures taken to minimize the risk to study participants, the potential risks are balanced by the anticipated benefits that may be afforded through vaccination with mRNA-1893.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objectives and Endpoints

Table 3: Primary Objectives and Endpoints

Objectives	Endpoints
Primary Safety	
To evaluate the safety, tolerability, and reactogenicity of 2 dose levels of mRNA-1893 Zika vaccine, administered in a 1-dose (CCI µg) or 2-dose schedule (CCI µg or CCI µg dose level) given 28 days apart, in comparison to a placebo control.	• Solicited local and systemic ARs through 7 days after each IP injection. • Unsolicited AEs through 28 days after each IP injection. • MAAEs throughout the entire study period. • SAEs and AESIs throughout the entire study period.
Primary Immunogenicity	
To evaluate the immunogenicity of 2 dose levels of mRNA-1893 Zika vaccine, administered in a 1-dose (CCI µg) or 2-dose schedule (CCI µg or CCI µg dose level) given 28 days apart, as measured by ZIKV-specific neutralization assay (PRNT), in comparison to a placebo control at Day 57.	• GMT of ZIKV-specific nAbs at Day 57, as measured by PRNT in all participants, in initially flavivirus-seronegative, and in initially flavivirus-seropositive participants. • Seroconversion from Day 1 to Day 57.

Abbreviations: AE = adverse event; AESIs = adverse events of special interest; AR = adverse reaction; GMT = geometric mean titer; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; nAb = neutralizing antibody; PRNT = plaque reduction neutralization test; SAE = serious adverse event; ZIKV = Zika virus.
Note: Seroconversion is defined as either an increase in ZIKV-specific nAb titer from below the LLOQ to a titer equal to or above LLOQ, or an increase of at least 4-fold in ZIKV-specific nAb titer in participants with pre-existing nAb titers (as measured by PRNT).

3.2. Secondary Objectives and Endpoints

Table 4: Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary Immunogenicity	
To evaluate the immunogenicity of 2 dose levels of mRNA-1893, as measured by ZIKV-specific neutralization assay (PRNT and MN), in comparison to a placebo control, in flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline.	• GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, and 57 (Day 57 only for MN), as measured by PRNT and MN. • GMT of ZIKV-specific nAbs in initially flavivirus-seronegative participants at Days 1, 8, 29, 36, and 57 (Day 57 only for MN), as measured by PRNT and MN. • GMT of ZIKV-specific nAbs in initially flavivirus-seropositive participants at Days 1, 8, 29, 36 and 57 (Day 57 only for MN), as measured by PRNT and MN. • GMFR of ZIKV-specific nAbs in all participants, in initially flavivirus-seronegative and in initially flavivirus-seropositive participants at Days 8, 29, 36, and 57, as measured by PRNT and MN. • Seroconversion from Day 1 (baseline) to Days 8, 29, 36, and 57 (Day 57 only for MN), as measured by PRNT and MN. • Seroresponse at Days 8, 29, 36, and 57 (Day 57 only for MN) in flavivirus-seronegative participants at baseline. • Increase from baseline of 2-fold or 4-fold in ZIKV-specific nAb titers at Days 8, 29, 36 and 57, as measured by PRNT and MN, in flavivirus-seropositive participants at baseline.

Abbreviations: GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantification; MN = microneutralization; nAb = neutralizing antibody; PRNT = plaque reduction neutralization test; ZIKV = Zika virus.
Notes: Seroconversion is defined as either an increase in ZIKV-specific nAb titer from below the LLOQ to a titer equal to or above LLOQ, or an increase of at least 4-fold in ZIKV-specific nAb titer in participants with pre-existing nAb titers (as measured by PRNT or MN).
Seroresponse is defined as an increase in ZIKV-specific nAb titer from below the LLOQ to greater than or equal to the LLOQ (as measured by PRNT or MN).

3.3. Exploratory Objectives and Endpoints

Table 5: Exploratory Objectives and Endpoints

Objectives	Endpoints
Exploratory	
To evaluate the duration of the humoral immune response of 2 dose levels of mRNA-1893 at Days 85, 196, 364, 532, and 700, as measured by ZIKV-specific neutralization assays (PRNT and MN), in comparison to a placebo control, in flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline.	• GMT of ZIKV-specific nAbs at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN. • GMT of ZIKV-specific nAbs at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seronegative participants at baseline. • GMT of ZIKV-specific nAbs at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seropositive participants at baseline. • GMFR of ZIKV-specific nAbs in all participants, in initially flavivirus-seronegative, and in initially flavivirus-seropositive participants at Day 85, 196, 364, 532, and 700, as measured by PRNT and MN. • Seroconversion[1] from Day 1 (baseline) to Days 85, 196, 364, 532, and 700, as measured by PRNT and MN. • Seroresponse[2] at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seronegative participants at baseline. • Increase from baseline of 2-fold or 4-fold in ZIKV-specific nAb titers at Days 85, 196, 364, 532, and 700, as measured by PRNT and MN, in flavivirus-seropositive participants at baseline. • Proportion of all participants, of baseline flavivirus-seronegative participants, and of baseline flavivirus-seropositive participants with a ZIKV-specific nAb titer equal or greater than a nAb titer defined as a protective level in an animal model, at baseline, and Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by PRNT. • Proportion of all participants, of baseline flavivirus-seronegative participants, and of baseline flavivirus-seropositive participants with a ZIKV-specific nAb titer equal or greater than a nAb titer defined as a protective level in an animal model, at baseline, and Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by MN.

Objectives	Endpoints
Exploratory	
To evaluate the humoral immunogenicity of 2 dose levels of mRNA-1893, as measured by RVP and by ligand binding assay, in comparison to a placebo control, in flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline.	• GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP. • GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP, in flavivirus-seronegative participants at baseline. • GMT of ZIKV-specific nAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP, in flavivirus-seropositive participants at baseline. • Seroconversion[1] from Day 1 (baseline) to Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP. • Seroresponse[2] at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP, in flavivirus-seronegative participants at baseline. • Increase from baseline of 2-fold or 4-fold in ZIKV-specific nAb titers at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by RVP, in flavivirus-seropositive participants at baseline. • GMC of ZIKV-specific serum ligand bAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay. • GMC of ZIKV-specific bAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seronegative participants at baseline. • GMC of ZIKV-specific bAbs at Days 1, 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seropositive participants at baseline. • Seroconversion[3] from Day 1 (baseline) to Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay. • Seroresponse[4] at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seronegative participants at baseline. • Increase from baseline 2-fold or 4-fold in bAb concentrations at Days 8, 29, 36, 57, 85, 196, 364, 532, and 700, as measured by ligand binding assay, in flavivirus-seropositive participants at baseline.

Objectives	Endpoints
Exploratory	
To evaluate the ZIKV-specific cellular immune response of 2 dose levels of mRNA-1893 in comparison to a placebo control in flavivirus-seronegative participants at baseline and in flavivirus-seropositive participants at baseline (CMI subset of participants).	• Frequency of ZIKV-specific T cells at Days 1 (baseline), 29, 36, 57, 196, 364, 532, and 700, as measured by intracellular cytokine staining assay and sequencing (CMI subset of baseline flavivirus-seronegative and -seropositive participants). • Frequency of ZIKV-specific B cells at Days 1 (baseline), 29, 36, 57, 196, 364, 532, and 700, as measured by ELISpot (CMI subset of baseline flavivirus-seronegative and -seropositive participants). • Additional assays to profile the T- and B-cell responses may also be included (CMI subset of baseline flavivirus-seronegative and -seropositive participants).
To assess the occurrence of flavivirus infections throughout the entire course of participation in the study in comparison to a placebo control.	• GMC of NS1-specific serum bAbs at Days 1 (baseline), 85, 196, 364, 532, and 700, as measured by ELISA. • Seroconversion[5] (NS1-specific bAbs) from Day 1 (baseline) to Days 85, 196, 364, 532, and 700.

Abbreviations: bAb = binding antibody; CMI = cell-mediated immunity; ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunosorbent spot; GMFR = geometric mean fold rise; GMT = geometric mean titer; GMC = geometric mean concentration; LLOQ = lower limit of quantification; MN = microneutralization; nAb = neutralizing antibody; NS1 = nonstructural protein 1; PRNT = plaque reduction neutralization test; RVP = reporter virus particle; ZIKV = Zika virus.

1 Seroconversion is defined as either an increase in ZIKV-specific nAb titer from below the LLOQ to a titer equal to or above LLOQ, or an increase of at least 4-fold in ZIKV-specific nAb titer in participants with pre-existing nAb titers (as measured by PRNT, MN, or RVP).

2 Seroresponse is defined as an increase in ZIKV-specific nAb titer from below the LLOQ to greater than or equal to the LLOQ (as measured by PRNT, MN, or RVP).

3 Seroconversion is defined as either an increase in ZIKV-specific bAb concentration from below the LLOQ to a concentration equal to or above LLOQ, or an increase of at least 4-fold in ZIKV-specific bAb concentration in participants with pre-existing bAb concentrations (as measured by ligand binding assay).

4 Seroresponse is defined as an increase in ZIKV-specific bAb concentration from below the LLOQ to greater than or equal to the LLOQ (as measured by ligand binding assay).

5 Seroconversion is defined as an increase in NS1-specific bAb concentration from below the LLOQ to a concentration equal to or above the LLOQ, or an increase of at least 4-fold in NS1-specific bAb concentration as measured by ELISA.

4. STUDY DESIGN

4.1. General Design

This is a Phase 2, randomized, observer-blind, placebo-controlled, dose confirmation study.

All participants will be evaluated for their eligibility (Section 4.1.1) for enrollment in the Vaccination Period and will be followed for approximately 6 months (Day 196) after their last IP injection (Section 4.1.2). Table 1 displays the Schedule of Assessments (SOA) for all participants through Day 196. All participants in all treatment arms will have the opportunity to continue to be followed as part of an approximately 24-month Extension Period (through Day 700) after their last IP injection (Section 4.1.3). Table 2 displays the SOA for participants who continue into the Extension Period through Day 700. The study design is illustrated in Figure 1.

A total of approximately 800 participants will be randomly assigned to receive either CCI µg or CCI µg mRNA-1893 administered as a 2-dose regimen with at least a 28-day interval between vaccinations (Treatment Arm A or Treatment Arm B), or CCI µg mRNA-1893 administered as a 1-dose regimen (Treatment Arm C), or placebo control administered as a 2-dose regimen with at least a 28-day interval between doses (Treatment Arm D) according to a 1:1:1:1 randomization ratio (ie, 200 participants per treatment arm with approximately 100 participants per baseline flavivirus serostatus in each treatment arm). Randomization was stratified by participants' baseline flavivirus serostatus assessed by a rapid dengue point-of-care test on site in the original protocol (dated 21 Feb 2021). Under the current protocol amendment, randomization will be stratified only by participants' region (continental US and Puerto Rico). All treatment arms will be enrolled in parallel. In order to maintain the blinding and to have the same study evaluation time point with both mRNA-1893 dose regimens relative to the last IP injection, participants randomly assigned to Treatment Arm C will be administered placebo at Day 1 and mRNA-1893 at Day 29 (Table 6).

Table 6: Treatment Arms

	Study Day	
	Day 1	**Day 29**
Treatment Arm A	mRNA-1893 CCI µg First vaccination	mRNA-1893 CCI µg Second vaccination
Treatment Arm B	mRNA-1893 CCI µg First vaccination	mRNA-1893 CCI µg Second vaccination
Treatment Arm C	Placebo	mRNA-1893 CCI µg First vaccination
Treatment Arm D	Placebo	Placebo

All participants will have up to 8 clinic visits (Days 0 [Eligibility Visit], 1 (baseline), 8, 29, 36, 57, 85, and 196) and 3 safety telephone calls (Days 112, 140, and 168). Participants who continue into the Extension Period will have 3 additional clinic visits at Days 364, 532, and 700.

The EOS is defined in Section 4.6. Participants who withdraw from further IP injection for any reason after their first IP injection but do not withdraw consent will complete all study procedures through the EOS Visit (Section 7).

4.1.1. Eligibility Evaluation

Up to 8 days prior to Visit 1 (Day 1), potential participants will be evaluated (interview and physical examination) to determine their eligibility to participate in the study according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively). The Eligibility (Day 0) and Baseline (Day 1) Visits may be combined on the same day.

4.1.2. Vaccination Period

All participants will receive IP injections at Visit 1 (Day 1) and Visit 3 (Day 29). Participants will be asked to complete an electronic diary (eDiary) to monitor solicited ARs for 6 days after each IP injection (Days 1 through 7 and Days 29 through 35) and to monitor unsolicited AEs for 28 days after each IP injection (Days 1 through 57). Serious AEs, AESIs and MAAEs will be monitored from Day 1 for approximately 6 months (Visit 10 [Day 196]) after the last IP injection.

Blood samples will be collected from all participants at Days 1 (baseline), 8, 29, 36, 57, 85, and 196 for the assessment of antibody-mediated immunogenicity. Blood samples will be collected from a subset of participants (cell-mediated immunity [CMI] subset) at Days 1 (baseline), 29, 36, 57, and 196 for peripheral blood mononuclear cell (PBMC) collection and assessment of cellular immunity. Blood samples collected from all participants at Days 85 and 196 will be used for detection of asymptomatic flavivirus infections.

In case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed), an additional blood sample will be collected to confirm the diagnosis via specific serology and reverse transcriptase polymerase chain reaction (RT-PCR), and clinical information will be carefully collected to evaluate the severity of the clinical case. Those symptoms are not specific; however, an association of acute fever onset with maculopapular rash, arthralgia, and conjunctivitis during the seasonal circulation of mosquitos must trigger samplings. Also, special attention will be paid to the reporting of neurological signs or symptoms evoking Guillain-Barré syndrome.

4.1.3. Extension Period

All participants enrolled who consent to continue into the Extension Period will return to the clinic for follow-up visits approximately every 6 months after the last IP injection (Days 364, 532, and 700). Serious AEs, AESIs, and MAAEs will be monitored throughout the Extension Period.

Blood samples will be collected at Days 364, 532, and 700 for the assessment of antibody-mediated immunogenicity. Blood samples will be collected from the CMI subset participants at Days 364, 532, and 700 for PBMC collection and assessment of cellular immunity. Blood samples collected from all participants at Days 364, 532, and 700 will be used for detection of asymptomatic flavivirus infections. Additional blood samples might also be collected during unscheduled visits for safety and/or immunogenicity purposes, at the discretion of the investigator.

As previously described in Section 4.1.2, in case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed) during the Extension Period, an additional blood sample will be collected to confirm the diagnosis via specific serology and RT-PCR, and clinical information will be carefully collected to evaluate the severity of the clinical case. Also, special attention will be paid to collect signs or symptoms possibly related to Guillain-Barré syndrome.

4.2. Scientific Rationale for Study Design

The design and dose levels proposed for this study (Study mRNA-1893-P201) are based on accumulated safety and immunogenicity data from the Phase 1 Study mRNA-1893-P101, which involved a total of 120 participants. Group unblinding interim analyses performed at Day 57 (ie, 28 days after the second vaccination) showed a safety profile compatible with a large use of the vaccine candidate and a production of ZIKV-specific nAbs at an SCR ranging from 12.5% (2.7% - 32.4%) to 75% (53.3% - 90.2%) after 1 vaccine administration and from 86.4% (65.1% - 97.1%) to 100% (85.8% - 100%) after the complete 2-dose vaccine administration.

Study mRNA-1893-P201 is intended to confirm the safety and immunogenicity trends observed during the Phase 1 study and aims to select the dose level for the Phase 3 program. Two dose levels, CCI µg and CCI µg, have been chosen as they appear to give the optimal response at Day 57 in terms of geometric mean titers (GMTs) and SCRs with a similar safety profile. The number of participants (200 per treatment arm with approximately 100 participants per baseline flavivirus serostatus in each treatment arm) planned for enrollment is consistent with a Phase 2 stage clinical study. The collection of solicited ARs and unsolicited AEs following vaccination is consistent with vaccine evaluation studies. Additionally, the 2-year follow-up will provide long-term safety profile information and documentation on the duration of the ZIKV-specific nAb response after a 1- or 2-dose regimen. It may also give the opportunity to evaluate occurrence of flavivirus infections,

mostly ZIKV and dengue, as the excontinental US sites are areas with potential for flavivirus circulation. The collection of blood at the given time points and the selection of the assays for the assessment of the ZIKV-specific immune response are based on experience from the preclinical and previous clinical studies.

4.3. Justification for the Choice of Study Population

It is anticipated that the specific immune response to a ZIKV vaccine candidate in participants who are baseline seronegative may be different from responses in those who are baseline seropositive for flavivirus. To explore the potential differences in safety and immunogenicity, this study will enroll healthy flavivirus-seronegative and flavivirus-seropositive participants.

Safety and immunogenicity evaluation in adults who are flavivirus seronegative at baseline and the most critical at risk population will confirm appropriateness of the dose selection in a larger number of participants.

As the Phase 1 study was predominantly performed in initially flavivirus-seronegative participants, this Phase 2 study will expand the safety data available in flavivirus-seropositive participants, in order to have enough confidence to administer mRNA-1893 without flavivirus serological knowledge in the large Phase 3 studies.

This Phase 2 study population will also target the age group in which the majority of cases occurred in previous epidemics (18 to 49 years of age) and a slightly older population extending up to 65 years, to account for the case distribution age for neurological sequalae such as Guillain-Barré syndrome that has been described with ZIKV.

4.4. Justification for Dose and Schedule

The 2 dose levels of mRNA-1893 tested in participants will be CCI µg and CCI µg based on the assessment of available safety and immunogenicity data from Study mRNA-1893-P101. The 2 dose levels will be administered as a 2-dose regimen (Treatment Arm A and B) with at least a 28-day interval between vaccinations that seems to give the optimal response. In addition, the CCI-µg dose will be administered as a single-dose regimen (Treatment Arm C) to generate safety and immunogenicity data that could be valuable in emergency situations, in military personnel and traveler populations who might need a rapid response, and also in populations living in endemic areas and with pre-existing immune response for which 1 vaccine administration might be sufficient.

4.5. Justification for the Use of Placebo

Because there are currently no licensed ZIKV vaccines available to be used as reference vaccine, 0.9% sodium chloride solution for injection (United States Pharmacopeia [USP] or British Pharmacopeia [BP]) (normal saline) will be used as placebo to maintain the blinding of the study and to serve as a control for the safety and immunogenicity assessments.

Moreover, to have the same study evaluation time point for primary evaluation with both mRNA-1893 dose regimens relative to the last IP injection, participants randomly assigned to Treatment Arm C will be injected at Day 1 with placebo and will receive mRNA-1893 at Day 29 (Table 6).

Those participants who receive saline placebo will have the same safety follow-up as those who receive the 1-dose or 2-dose mRNA-1893 regimen (Treatment Arm A and Treatment Arm B).

4.6. End of Study Definition

The EOS is defined as completion of the last visit of the last participant in the study or last scheduled procedure as shown in Table 1 and Table 2 for the last participant in the study globally.

Participants who do not consent to continue into the Extension Period will be considered to have completed the study if they have completed the EOS Visit approximately 6 months (Visit 10 [Day 196]) after the last IP injection. Participants who consent to continue into the Extension Period will be considered to have completed the study if they have completed the EOS Visit approximately 24 months (Day 700) after the last IP injection.

5. STUDY POPULATION

The study will enroll approximately 800 adult participants aged 18 through 65 years at baseline, including approximately 400 flavivirus-seropositive participants and 400 flavivirus-seronegative participants, who will receive mRNA-1893 or placebo.

A dengue rapid point-of-care test initially used to stratify study participants has been discontinued. After this protocol amendment, all participants will be stratified based on geographic region, assuming most of the baseline seronegatives will come from continental US sites and the baseline seropositives from Puerto Rico. The confirmation will be done based on flavivirus serology testing (dengue immunoglobulin G [IgG] and immunoglobulin M [IgM], West Nile IgG and IgM) performed on a blood sample collected prior to administration of the first vaccination with a goal of an approximately equal distribution of participants among seronegative and seropositive participants within each treatment group.

The planned participant distribution is presented by treatment arm in Table 7.

Table 7: Participant Distribution by Treatment Arm

Investigational Product	Baseline Flavivirus-Seronegative Participants	Baseline Flavivirus-Seropositive Participants	Total
mRNA-1893 CCI µg (Treatment Arm A)	100	100	200
mRNA-1893 CCI µg (Treatment Arm B)	100	100	200
mRNA-1893 CCI µg (Treatment Arm C)	100	100	200
Placebo (Treatment Arm D)	100	100	200
Total	400	400	800

Upon completion of all eligibility evaluations, the investigator will review the inclusion/exclusion criteria for each participant to determine if the participant is eligible for enrollment in the study. Participants who meet all eligibility criteria will be enrolled in the study.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male or female participant aged 18 through 65 years at the time of consent.

2. Understands and agrees to comply with the study procedures and provides written informed consent.
3. According to investigator assessment, is in good general health and can comply with study procedures.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to the eligibility evaluation without an alternative medical cause). The follicle-stimulating hormone (FSH) level may be measured at the discretion of the investigator to confirm postmenopausal status.
5. Female participants of childbearing potential may be enrolled in the study if the participant: 1) has a negative pregnancy test at the Eligibility Visit and on the day of the first IP injection, 2) has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first IP injection, 3) has agreed to continue adequate contraception through 3 months following the last IP injection, and 4) is not currently breastfeeding.

   Adequate female contraception is defined as consistent and correct use of a Food and Drug Administration (FDA)-approved contraceptive method in accordance with the product label (Table 16). Examples are as follows:

   - Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide.
   - Intrauterine device.
   - Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route.
   - Sterilization of a female participant's monogamous male partner prior to entry into the study.

   Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Is acutely ill or febrile (temperature ≥ 38.0°C/100.4°F) on the day of the first or second vaccination. Participants meeting either of these criteria may be rescheduled for enrollment/randomization if the event resolves within the vaccination window.
2. Had prior administration of a ZIKV vaccine candidate during a clinical study investigation.
3. Had prior administration of a marketed dengue vaccine or dengue vaccine candidate under clinical study investigation.
4. Has a body mass index (BMI) from ≤ 18 or ≥ 35 kg/m^2.
5. History of myocarditis, pericarditis, or myopericarditis.
6. History of a diagnosis or condition that, in the judgement of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. “Clinically unstable” is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to screening and includes ongoing work-up of an undiagnosed illness that could lead to a new diagnosis or condition.
7. Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that in the opinion of the investigator, might pose a risk due to participation in the study or could interfere with the interpretation of study results.
8. Has a known or suspected autoimmune disease, including hypothyroidism in relation to autoimmune thyroiditis.
9. Has a history of progressive or severe neurologic disorder or a history of neuroinflammatory disease such as Guillain-Barré syndrome.
10. Has a history of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine, including an mRNA vaccine or any components of an mRNA vaccine.
11. Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
12. Has been diagnosed with malignancy within the previous 10 years (excluding nonmelanoma skin cancer).
13. Has received or plans to receive a nonstudy vaccine (including authorized or approved vaccines for the prevention of COVID-19) ≤ 28 days prior to the first IP injection or within

28 days prior to or after any IP injection. Licensed influenza vaccine received within 14 days prior to the first IP injection or plans to receive a licensed influenza vaccine 14 days prior to through 14 days following each IP injection are not exclusionary.

14. Has a known or suspected impairment or alteration of immune function including the following:
    a. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks or ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
    b. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks or ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1.
    c. Receipt of immunosuppressive therapy within 3 months prior to Day 1 or planned during the 7-month period following study enrollment.
    d. Receipt of immunostimulants within 60 days prior to Day 1.
    e. Receipt of parenteral, epidural, or intra-articular immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to Day 1 or planned during the 7-month period following study enrollment.
    f. HIV infection or HIV-related disease.
    g. Genetic immunodeficiency.
15. Has received systemic immunoglobulins or blood products within 3 months prior to the day of enrollment.
16. Has donated ≥ 450 mL of blood products within 28 days of the Day 1 Visit.
17. Has participated in an interventional clinical study within 28 days prior to the day of enrollment or plans to do so while enrolled in this study.
18. Is an immediate family member or household member of study personnel.

5.3. Lifestyle Restrictions

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes screen failure details, eligibility criteria, and any SAEs.

6. INVESTIGATIONAL PRODUCT

6.1. Investigational Products Administered

mRNA-1893 consists of an mRNA sequence that encodes the full prME structural polyprotein of ZIKV in a liposomal formulation.

The LNP formulation includes 4 lipid excipients: SM-102, a proprietary ionizable amino lipid, and the commercially available lipids: cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine; and 1,2-dimyristoyl-sn-glycerol, methoxypolyethyleneglycol (Mui et al 2013). In addition, the undiluted (0.20 mg/mL) Drug Product contains CCI [redacted].

The placebo is 0.9% sodium chloride solution for injection, USP or BP.

The characteristics of the IPs are presented in Table 8.

Table 8: Investigational Products Administered

	Treatment Arm A	Treatment Arm B	Treatment Arm C (2nd Administration)	Treatment Arm C (1st administration) and Treatment Arm D (1st and 2nd administrations)
Investigational Product Name:	mRNA-1893	mRNA-1893	mRNA-1893	Placebo
Type:	Vaccine	Vaccine	Vaccine	Normal saline
Unit Dose Strengths:	0.20 mg/mL	0.20 mg/mL	0.20 mg/mL	0.9% sodium chloride solution for injection (USP or BP)
Dosage Levels:	CCI µg in 0.5 mL (Days 1 and 29)	CCI µg in 0.5 mL (Days 1 and 29)	CCI µg in 0.5 mL (Day 29)	Treatment Arm C: 0.5 mL (Day 1) Treatment Arm D: 0.5 mL (Days 1 and 29)
Route of Administration:	IM injection	IM injection	IM injection	IM injection
Source:	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee	Provided by the Sponsor or designee for use as both a placebo and a diluent to mRNA-1893
Packaging and Labeling:	mRNA-1893 will be provided as a 0.20 mg/mL dispersion in 2R glass vials labeled as required per country requirement.	mRNA-1893 will be provided as a 0.20 mg/mL dispersion in 2R glass vials labeled as required per country requirement.	mRNA-1893 will be provided as a 0.20 mg/mL dispersion in 2R glass vials labeled as required per country requirement.	The 0.9% sodium chloride will bear a commercial label and any country-specific requirements.

Abbreviations: BP = British Pharmacopeia; IM = intramuscular; USP = United States Pharmacopeia.

6.2. Preparation, Handling, Storage, and Accountability of Investigational Products

The Sponsor or designee is responsible for the following:

- Supplying the IPs.
- Confirming the appropriate labeling of IP, such that it complies with the legal requirements of each country where the study is to be performed.

The investigator is responsible for acknowledging the receipt of the IPs by a designated staff member at the site, including the following:

- Confirming appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

- Ensuring that only participants enrolled in the study will receive mRNA-1893 and only authorized unblinded site staff will supply or administer the IP. All IPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized unblinded site staff.
- Ensuring the appropriate dose level of mRNA-1893 is prepared using aseptic techniques (vaccine diluted with 0.9% sodium chloride solution for injection [USP or BP] to a concentration for delivery of the specified dose level in a volume of 0.5 mL).
- Maintaining IP records (ie, receipt, accountability, reconciliation, and final disposition records) using the Drug Accountability Log. These logs must be available for inspection at any time.

As the appearance of mRNA-1893 and placebo differs, only designated unblinded personnel qualified to prepare and/or administer vaccine will be aware of the treatment assignment (Section 6.3.2).

Further description of the IPs and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IPs is provided in the Study mRNA-1893-P201 Pharmacy Manual.

6.2.1. Investigational Product Preparation

mRNA-1893 will be provided as a 0.20 mg/mL dispersion in 2R glass vials labeled as required per country requirement. The vaccine will be diluted to a concentration for delivery of the specified dose level in a volume of 0.5 mL.

6.2.2. Investigational Product Administration

The IP will be administered as an IM injection into the deltoid muscle, and each dose will have a volume of 0.5 mL. Preferably, the first dose should be injected into the nondominant arm and the second dose should be injected into the same arm as the first dose.

The IP will be prepared for injection as a single 0.5-mL dose for each participant based on the treatment arm and randomization assignment, as detailed in the Study mRNA-1893-P201 Pharmacy Manual. Unblinded pharmacy personnel, who will not participate in any other aspect of the study, will perform IP accountability, dose preparation, and administration. The investigator will designate an unblinded clinical team member to provide oversight to the vaccination so that it proceeds according to the procedures stipulated in this study protocol and the Study mRNA-1893-P201 Pharmacy Manual. Study-specific training will be provided.

At each visit when IP is administered, participants will be monitored for a minimum of 30 minutes after IP injection. Assessments will include vital sign measurements and monitoring for immediate local or systemic reactions (Table 1).

Eligibility for subsequent IP injection is determined by following the criteria outlined in Section 7.1.

The study site will be appropriately staffed, and staff will be trained and experienced in delivering emergency resuscitation and will have stocked rescue medications (such as epinephrine, steroids, antihistamines, and intravenous fluids) should any severe AR (eg, anaphylaxis or urticaria) occur that requires immediate intervention.

Further instructions for the preparation and administration of mRNA-1893 are described in the Study mRNA-1893-P201 Pharmacy Manual.

6.2.3. Investigational Product Packaging and Labeling

All IPs used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, US Title 21 Code of Federal Regulations (CFR), Good Manufacturing Practice guidelines, ICH GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

A 0.9% sodium chloride solution for injection (USP or BP) (normal saline) for use as placebo and mRNA-1893 preparation will contain a commercial label and country requirements as necessary.

6.2.4. Investigational Product Storage

mRNA-1893 must be stored at -25ºC to -15°C (-13ºF to 5ºF). mRNA-1893 must be received by designated unblinded personnel at the study site, handled and stored safely and properly, kept in a secured location with restricted access (unblinded pharmacy staff only), and protected from moisture and light until it is prepared for administration.

The 0.9% sodium chloride solution for injection (USP or BP) must be stored at 20ºC to 25ºC (68ºF to 77ºF) in a restricted access area (unblinded pharmacy staff only).

6.2.5. Investigational Product Accountability

The unblinded designee must maintain an accurate record of the shipment receipt, the inventory at the site, dispensing of study treatment, and the return to the Sponsor or alternative disposition of used/unused products in a drug accountability log. Drug accountability will be noted by the unblinded clinical research associate (CRA) during site visits and at the completion of the study. For further direction, refer to the Study mRNA-1893-P201 Pharmacy Manual.

6.2.6. Investigational Product Handling and Disposal

The designated unblinded CRA will reconcile the IP at the interim monitoring visit and at the end of the study for compliance. Once fully reconciled at the site, the IP can be destroyed at the investigational site or by a Sponsor-selected third party, as appropriate.

The IP may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A Certificate of Destruction must be obtained and sent to the Sponsor or designee. For further direction refer to mRNA-1893-201 Pharmacy Manual.

6.3. Randomization and Blinding

6.3.1. Randomization

The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT), in accordance with pre-generated randomization schedules. Approximately 800 participants will be randomized in parallel according to a 1:1:1:1 randomization ratio to the 4 treatment arms. Randomization was stratified by participants' baseline flavivirus serostatus under the original protocol. Under this protocol amendment, randomization will be stratified only by participants' region (continental US and Puerto Rico). Only the unblinded pharmacy personnel (Section 6.3.2) will have controlled access to which arm the participant is randomly assigned.

6.3.2. Blinding

This is an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until the electronic data capture (EDC) is locked and CSR has been written, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to IP accountability procedures and will prepare and administer mRNA-1893 or placebo to all participants. These pharmacy personnel will have no study functions other than IP management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of the IP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency (Section 6.3.3).
- Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that sites are following all proper IP accountability, preparation, and administration procedures.
- An unblinded statistical and programming team will perform the preplanned Day 57 interim analysis (IA) (Section 9.5). A limited number of Sponsor team members will be

pre-specified to be unblinded to the IA results and will not communicate the results of interim analyses to the blinded investigators, study site staff, clinical monitors, or participants.

The IP assignment will be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. Only delegated unblinded site staff will conduct the vaccination procedure. Once each vaccination is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

Study site blinded staff will remain blinded to individual treatment assignments until the end of the study.

6.3.3. Unblinding

Except in the case of medical necessity, a participant's treatment assignment should not be unblinded without the approval of the Sponsor. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the treatment assignment will affect that participant's clinical management. In the event of a medical emergency requiring identification of individual treatment assignment, the investigator will make every attempt to contact the Sponsor medical lead or designee to explain the need for unblinding within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for unblinding, and the names of the personnel involved. The investigator (or designee) will have access to unblind participants within IRT. All unblindings will be tracked via an audit trail in IRT and documented in the final study report.

If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

The Sponsor will remain blinded to IP assignment throughout the treatment phase for each individual treatment arm of the study up until each specified time point for interim analyses, as outlined in Section 9.5.

6.4. Investigational Product Compliance

All doses of IP will be administered at the study site under direct observation of unblinded pharmacy personnel and appropriately recorded (date and time) in the electronic case report forms (eCRFs). Unblinded pharmacy personnel will confirm that the participant has received the entire dose of IP. If a participant does not receive IP or does not receive all of the planned doses, the reason for the missed dose will be recorded.

Participants who miss the second vaccination due to noncompliance with the visit schedule will still be required to follow the original visit and testing schedule as described in the protocol. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of IP will remain in the study and complete all safety and immunogenicity assessments required through the scheduled EOS.

The study site is responsible for ensuring participants comply with the study windows allowed. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined time window (Table 1 and Table 2). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (eg, eDiary review for reactogenicity, immune testing, as applicable).

6.5. Prior and Concomitant Medications and Therapies

6.5.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

6.5.2. Concomitant Medications and Therapies

At each study visit the following concomitant medications and vaccines must be recorded in the eCRF:

- All concomitant medications administered from the Eligibility Visit through 28 days after the last IP injection.
- Any nonstudy vaccines administered during the period starting 28 days before the first IP injection and ending at the last study visit.
- Any concomitant medications and vaccines listed in Section 6.5.3.
- Any concomitant medications and vaccines relevant to an SAE/AESI or administered from the signing of the informed consent form (ICF) through the last study visit for the treatment of an SAE/AESI.
- Any antipyretic or analgesic to treat or prevent fever or pain within 7 days after IP injection, including day of injection.

- Participants will be asked to record in the eDiary any antipyretic or analgesic taken to treat or prevent fever or pain within 7 days (including the day of injection) after IP injection. Reported antipyretic or analgesic medications should be recorded in the source document by the site staff during the post-IP injection study visits or via other participant interactions (eg, telephone calls).

6.5.3. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses

The use of the following concomitant medications and nonstudy vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the Per-Protocol (PP) analyses. Analysis sets are described in Section 9.3.

- Any investigational or nonregistered product (drug or vaccine) other than the IP used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the Vaccination Period or 60 days after the first IP injection. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the Vaccination Period or 60 days after the first IP injection (eg, infliximab).
- A nonstudy vaccine not foreseen by the study protocol administered during the Vaccination Period through 28 days after each IP injection.
- Immunoglobulins and/or any blood products administered up to Day 57.

6.6. Intervention After the End of the Study

Any SAE/AESI and unexpected AEs occurring after the end of the study and considered to be caused by the IP must be reported to the Sponsor.

7. DELAY OR DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

7.1. Criteria for Delay of Investigational Product Administration and Contraindication to Subsequent Administrations

Prior to receiving a second vaccination, participants will be reassessed to ensure that they continue to meet eligibility requirements as outlined below.

The following events in a participant constitute absolute contraindications to any further administration of the IP to that participant. If any of these events occur during the study, the participant must not receive additional doses of IP but will be encouraged to continue study participation for safety through approximately 6 months following the vaccination (Section 7.2):

- Anaphylaxis or systemic hypersensitivity reaction following the administration of IP.
- Any SAE or AESI judged by investigator or Sponsor to be related to IP.
- Pregnancy.
- Any clinically significant change in vital sign measurements or general condition that, in the opinion of the investigator, poses an additional risk to the participant if he/she continues to participate in the study.

The following events constitute contraindications to administration of IP at certain points in time, and if any of these events occur at the time scheduled for injection, the participant may be injected at a later date, within the time window specified in Table 1, or the participant may be withdrawn from dosing at the discretion of the investigator (Section 7.3):

- Acute moderate or severe infection with or without fever at the time of injection.
- Fever defined as body temperature ≥ 38.0°C (100.4°F) at the time of injection.

Participants with a minor illness without fever, as assessed by the investigator, can be administered IP. Participants with a fever of 38.0°C (100.4°F), or higher will be contacted within the time window acceptable for participation and re-evaluated for eligibility.

7.2. Discontinuation of Investigational Product

A "withdrawal" from the IP refers to any participant who does not receive the vaccination series. The investigator should make all efforts to ensure that the participants remain in the study to ensure a proper safety follow-up and medical care if needed, and document reason for participant withdrawal from study injection.

Information relative to premature discontinuation of the IP will be documented in the eCRF. The investigator will document which of the following reasons was responsible for withdrawal:

- SAE.
- AESI.
- AE (non-SAE).
- Dosing error.
- Other (specify).

Participants who withdraw from further study injection for any reason after their first dose but do not withdraw consent will complete all study procedures through EOS, as outlined in Table 1.

7.3. Participant Withdrawal from the Study

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive.

Participants who are withdrawn will not be replaced.

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit foreseen in the protocol.

All data collected until the date of withdrawal or last contact of the participant will be used for the analysis, including collected specimens.

A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

Investigators will attempt (eg, 3 documented telephone calls) to contact those participants who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a participant from the study was made by the participant or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE (specify).
- Death.
- Lost to follow-up (LTFU).

- Physician decision (specify).
- Pregnancy.
- Protocol violation.
- Study terminated by Sponsor.
- Withdrawal of consent by participant (specify).
- Other (specify).

Participants who are withdrawn from the study because of SAEs/AESIs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants who are withdrawn from the study as a result of an SAE, AESI or AE until resolution of the event.

Participants who withdraw from the study may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If participants withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

7.4. Lost to Follow-Up

A participant will be considered LTFU if he/she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 documented telephone calls and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed. The date of withdrawal/LTFU should be the date of last contact with the participant where safety status of the participant was assessed (eg, clinic visit, telephone call).

7.5. Circumstances to Delay or Discontinue the Study Independent of Investigational Product and Participant

There are instances such as public health emergencies or natural disasters that may directly affect the initial plan for the study conduct. Those circumstances may correspond but are not limited to new emerging infectious diseases such as the current COVID-19 pandemic. Cognizant of the challenges that may arise from those situations, an operational plan will be elaborated in a separate document describing potential repercussions, approaches to protect study participants, and factors to consider for decision to suspend or continue the ongoing study. This document follows FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency updated on 03 Jun 2020 (DHHS 2020). Refer also to Section 8.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and time points are summarized in the SOAs (Table 1 and Table 2). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in Table 1 and Table 2, is essential and required for study conduct.

Before performing any study procedures, all potential participants will sign an ICF (Section 11.1.6). Potential participants will be evaluated (interview and physical examination) to determine their eligibility to participate in the study according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively). All eligibility evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. If a participant is not enrolled in the study, the reason for eligibility failure must be recorded. The investigator will maintain a log to record details of all participants evaluated and to confirm eligibility or record reasons for failure, as applicable.

A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, new or ongoing AEs, or a suspicion of a flavivirus infection. The site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or to follow-up on ongoing or outstanding issues.

In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency updated on 03 Jun 2020 (DHHS 2020), investigators may convert study site visits to telemedicine visits with the approval of the Sponsor. If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Day 0, Day 1, and Day 29 Visits, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor. If neither a participant visit to the study site nor a home visit to the participant is possible (with the exception of Day 0, Day 1, and Day 29 Visits), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls scheduled on Days 112 through 168 (Table 1). Such action should be taken to protect the safety and well-being of study participants and clinical site staff or to comply with state or municipal mandates.

8.1. Demographics and Other Baseline Characteristics

Demographic information (eg, sex, age, race, and ethnicity) and other baseline characteristics (eg, weight and height) will be recorded on the appropriate eCRF page during the eligibility evaluation.

The medical history of each participant will be obtained by interviewing the participant or by reviewing the participant's medical records. Any pre-existing conditions or signs and/or symptoms present prior to the signature of the ICF must be included on the Medical History page of the eCRF.

8.2. Clinical Laboratory Assessments

8.2.1. Baseline and Safety Laboratory Assessments

There are no screening criteria based on the flavivirus serostatus, meaning all participants are enrolled regardless of serostatus. However, this baseline flavivirus status will be confirmed by serology testings (dengue IgG and IgM, West Nile IgG and IgM) performed on a blood sample collected prior to administration of the first vaccination in order to eventually ensure that an approximate equal distribution of participants among subgroups is respected for the statistical analysis.

A point-of-care urine pregnancy test will be performed at the Eligibility Visit and before each IP injection (or at any time at the discretion of the investigator) for all female participants of childbearing potential.

The FSH level may be measured at the discretion of the investigator to confirm menopausal status.

There are no screening safety laboratory tests at the time of the eligibility evaluation of the participant. However, additional tests may be performed for safety reasons at any time during the study if determined necessary by the investigator or required by local regulations. Specifically, if the participant presents with signs or symptoms evoking a flavivirus infection, standard-of-care tests and treatment will apply, and results will be reported in the source documents and in the AE section of the eCRF.

8.3. Immunogenicity and Efficacy Assessments

8.3.1. Immunogenicity Assessments

Blood samples for analysis of the immunogenicity will be collected as described in Table 1 and Table 2. On Days 1 and 29, blood samples for immunogenicity assessment will be collected before vaccination.

The approximate blood volumes to be collected from each participant during the study are presented in Section 8.4.

The following antibody-mediated immunogenicity assessments will be performed:

- Serum ZIKV-specific nAb titers, as measured by PRNT assay, MN assay, and RVP assay.
- Serum ZIKV-specific bAb concentrations, as measured by ligand binding assay.

The following CMI assessments will be performed with the additional blood samples collected for PBMC isolation from the CMI subset participants (Table 1 and Table 2):

- Frequency of ZIKV-specific T cells, as measured by ICS assay and sequencing.
- Frequency of ZIKV-specific B cells, as measured by ELISpot.
- Other techniques that may be relevant to assesses the profile characteristics of the ZIKV-specific T- and B-cell responses may be also included.

Sample aliquots will be designed to ensure that backup samples are available and that adequate vial volumes may allow further 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.

Testing will be performed in laboratories designated by the Sponsor.

8.3.2. Efficacy Assessments

Blood samples for detection of asymptomatic flavivirus infection will be collected as described in Table 1 and Table 2. Asymptomatic flavivirus infections will be assessed through quantification of nonstructural protein 1-specific bAbs, as measured by enzyme-linked immunosorbent assay (ELISA).

In case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed), an additional blood sample will be collected to confirm the diagnosis via specific serology (IgM antibody capture ELISA and virus neutralization assay) and RT-PCR.

8.4. Total Blood Volume

All samples (blood, serum, or PBMCs) must be collected in accordance with acceptable laboratory procedures and will be processed, labeled, and stored in accordance with the instructions in the Laboratory Manual.

The approximate blood volumes to be collected from each participant during the Vaccination Period and Extension Period are provided in Table 9 and Table 10, respectively.

Table 9: Total Planned Approximate Blood Volumes for the Vaccination Period

Assessment	Approximate Blood Volume per Sample	Scheduled Number of Collections[1]	Total Approximate Amount of Scheduled Blood Volume
Flavivirus status baseline level by ELISA[2]	8 mL	1	8 mL
Serum neutralizing antibodies against ZIKV by neutralization assays	12 mL	7	84 mL
Serum binding antibodies against ZIKV by ELISA			
Antibodies against envelope- and NS1-based antigens by ELISA (for asymptomatic ZIKV case detection)			
Quantification and qualification of ZIKV-specific T cells and ZIKV-specific B cells (CMI subset of participants)[3]	88 mL (for PBMC collection)	5	440 mL
Participant Approximate Maximum Total[4]			**532 mL**
Exploratory research[6]	60 mL	1	60 mL
Only in Case of Signs or Symptoms Suggesting a Flavivirus Infection[5]			
Dengue by serology and RT-PCR	2 mL	–	2 mL
Zika by serology and RT-PCR	6 mL	–	6 mL

Abbreviations: CMI = cell-mediated immunity; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; IgM = immunoglobulin M; NS1 = nonstructural protein 1; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcription polymerase chain reaction; ZIKV = Zika virus.

1 Additional blood collections may be required at the discretion of the investigator to follow-up on abnormal results.

2 Flavivirus testing by ELISA at baseline will include testing for dengue and West Nile IgG and IgM measurements.

3 Peripheral blood mononuclear cells will be isolated from blood samples collected from the CMI subset participants, which is a subset of participants selected from approximately 4 sites that have experience in human cell collection.

4 The approximate blood volume of 532 mL includes the volume collected for the PBMC collection and other assays in the CMI subset participants over a period of 6 months.

5 In case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed), an additional blood sample will be collected to confirm the diagnosis via specific serology and RT-PCR.

6 On Day 57, an additional blood sample (60 mL) will be collected from participants enrolled at 1 US site for exploratory research, in particular for animal challenge studies (Section 11.1.10).

Table 10: Total Planned Approximate Blood Volumes for the Extension Period

Assessment	Approximate Blood Volume per Sample	Scheduled Number of Collections[1]	Total Approximate Amount of Scheduled Blood Volume
Serum neutralizing antibodies against ZIKV by neutralization assays	12 mL	3	36 mL
Serum binding antibodies against ZIKV by ELISA			
Antibodies against envelope- and NS1-based antigens by ELISA (for asymptomatic ZIKV case detection)			
Quantification and qualification of ZIKV-specific T cells and ZIKV-specific B cells (CMI subset of participants)[2]	88 mL	3	264 mL
Participant Approximate Maximum Total[3]			**300 mL**
Only in Case of Signs or Symptoms Suggesting a Flavivirus Infection[4]			
Dengue by serology and RT-PCR	2 mL	–	2 mL
Zika by serology and RT-PCR	6 mL	–	6 mL

Abbreviations: CMI = cell-mediated immunity; ELISA = enzyme-linked immunosorbent assay; NS1 = nonstructural protein 1; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcription polymerase chain reaction; ZIKV = Zika virus.

1 Additional blood collections may be required at the discretion of the investigator to follow-up on abnormal results.

2 Peripheral blood mononuclear cells will be isolated from blood samples collected from the CMI subset participants, which is a subset of participants selected from approximately 4 sites that have experience in human cell collection.

3 The approximate blood volume of 300 mL includes the volume collected for the PBMC collection and the other assays in the CMI subset participants over a period of 18 months with a 6-month periodicity; for the other participants, the blood volume collected is approximately 36 mL.

4 In case of signs or symptoms suggesting a flavivirus infection (mostly dengue and Zika in the areas where the study will be performed), an additional blood sample will be collected to confirm the diagnosis via specific serology and RT-PCR.

8.5. Safety Assessments

The planned time points for all safety assessments are provided in Table 1 and Table 2.

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs (Section 11.2.3; Appendix 2) that occur during the 7 days following each IP injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 8.5.1).

- Unsolicited AEs observed or reported during the 28 days following each IP injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol-defined solicited ARs (Section 11.2.3; Appendix 2). Unsolicited AEs will be captured during safety telephone calls or at site visits and recorded on the participant's AE CRF.
- AEs leading to discontinuation from IP and/or study participation throughout the entire study duration (up to Day 700).
- MAAEs (Section 11.2.4; Appendix 2) from Day 1 throughout the entire study duration (up to Day 700).
- SAEs and AESIs (Section 11.2.2; Appendix 2) from Day 1 throughout the entire study duration (up to Day 700).
- Physical examination findings (Section 8.5.3).
- Vital sign measurements (Section 8.5.4).

8.5.1. Electronic Diary Assessments

At the time of consent, participants must confirm they are willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. This study will utilize the Medidata Patient Cloud Application as the eDiary. This application allows for real-time data collection on a fully audited and 21 CFR Part 11-compliant system directly from participants, ensuring that data are attributable, legible, contemporaneous, original, and accurate at all critical collection points. As the key diary data capture is unsupervised in participants' own homes, through the use of programmed data entry windows and time stamps, the Patient Cloud application ensures the data are collected as per the trial design. By leveraging electronic data collection, Medidata's Patient Cloud Application enables participants an easier way to collect data - seamlessly integrated into their daily routines - while similarly allowing site staff, contract research organizations (CROs), and sponsors immediate access to critical data actions. Before enrollment on Day 1, the participant will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 11.2.3; Appendix 2) on Day 1.

At each vaccination visit, participants will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature and ruler usage to measure injection site erythema and swelling/induration (hardness). Oral temperature is the preferred route of measurement.

At each vaccination visit, participants will record data into the eDiary starting at least 30 minutes after IP injection under supervision of the study site staff to ensure successful entry of assessments. The site staff will perform any retraining as necessary. Study participants will continue to record data in the eDiary after they leave the clinic, preferably in the evening and at the same time each day, on the day of injection, and for 6 days following each injection.

Participants will record the following data in the eDiary:

- Solicited local and systemic ARs (Section 11.2.3; Appendix 2) that occur on the day of each dose and during the 7 days after injection (ie, the day of injection and 6 subsequent days). Any solicited AR that is ongoing beyond Day 7 will be recorded until it is no longer reported, not to exceed 28 days after each injection. Solicited ARs recorded in eDiaries beyond Day 7 should be reviewed by study site staff either during the next scheduled telephone call or at the next study site visit (Table 1 and Table 2).
- Daily oral body temperature measurement should 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 should be recorded.
- Measurements, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- All medications taken on the day of each dose and during the 28 days after injection (ie, the day of injection and 27 subsequent days). Participants will be queried by the eDiary whether any medications were taken to treat or prevent pain or fever on a day of injection or for the 6 subsequent days.

The eDiaries will be the main source documents allowed for solicited local or systemic ARs (including body temperature measurements). Participants will be instructed to complete eDiary entries daily. If assessments are not recorded for a given day, the participant will have a limited time window on the following day to complete qualitative assessments for the previous day, excluding measurements of body temperature and of any injection site erythema or swelling/induration. Any new safety information reported during safety telephone calls or at site visits (including a solicited AR) not already captured in the eDiary will be described in the source documents as a verbally reported event. Any solicited AR reported in this manner must be entered on the Reactogenicity page of the eCRF.

Procedures for transferring eDiary data to the eCRF are presented in the Study mRNA-1893-P201 Study Manual. Study site staff will review eDiary data with participants at the Day 8 and Day 36 Visits.

8.5.2. Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. The participant will be interviewed according to the script, and information will be collected about the occurrence of any MAAEs, SAEs, AESIs, or AEs leading to study withdrawal, concomitant medications associated with those events, and any nonstudy vaccinations.

The timing of the safety telephone calls is provided in Table 1.

All safety information described by the participant must be documented in source documents and not documented on the script used for the safety telephone contact.

8.5.3. Physical Examination

A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems according to standard medical practice. Weight and height will be recorded and BMI will be calculated (body weight [kg] ÷ height $[m]^2$) during the eligibility evaluation.

A symptom-directed physical examination will be performed at the discretion of the investigator each time the participant is in the clinic when a full physical examination is not otherwise specified. Symptom-directed physical examinations will include, at a minimum, inspection of the general status of the participant, according to standard medical practice. Additional elements of the physical examination should be added on the basis of symptoms described during the interview of the participant. Prior to IP injection and at follow-up visits, female participants should also be queried for new onset of menarche.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Treatment of any abnormality observed during physical examination should be performed according to local medical practice outside the study or by referral to an appropriate healthcare provider at the discretion of the investigator. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the eCRF.

8.5.4. Vital Sign Measurements

Vital sign measurements will include body temperature (preferred route is oral), systolic and diastolic blood pressure, heart rate, and respiratory rate. The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be collected prior to study procedures and at least 30 minutes after IP injection, prior to discharge of the participant from the study site.

Febrile participants at Day 1 and Day 29 Visits (fever is defined as a body temperature ≥ 38.0°C/100.4°F) may be rescheduled within the relevant window periods.

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 13) of Grade 3 or greater, the abnormal value and grade will be documented on the AE page of the eCRF (unless there is another known cause of the abnormality that would result in an AE classification). The investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at baseline, is considered stable, or until the investigator determines that follow-up is no longer medically necessary.

8.6. Adverse Events and Serious Adverse Events

The definitions and procedures for the recording, evaluation, follow-up, and reporting of AEs (solicited ARs, unsolicited AEs, and MAAEs) and SAEs are presented in Appendix 2.

Adverse events will be reported by the participant. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the administration of IP or study procedures, or that caused the participant to discontinue the study.

8.6.1. Time Period and Frequency for Collecting AE and SAE Information

Medical occurrences that begin before the first vaccination with mRNA-1893 but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF, not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

The time periods for collection, recording, and reporting of solicited ARs, unsolicited AEs, and SAEs are found in Appendix 2.

Adverse events may be collected as follows:

- Observing the participant.

- Receiving an unsolicited complaint from the participant.
- Questioning the participant in an unbiased and nonleading manner.

Solicited ARs will be collected from the day of injection through 6 days after each IP injection (Days 1 through 7 and Days 29 through 35). Other (unsolicited) AEs will be collected from the day of injection through 28 days after each IP injection (Days 1 through 29 and Days 29 through 57).

Serious AEs will be collected from the first IP injection until the last follow-up visit after the last IP injection at the time points specified in the SOAs (Table 1 and Table 2).

All SAEs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Section 11.2.11. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

An abnormal value or result from a clinical or laboratory evaluation (eg, a radiograph, an ultrasound, or an electrocardiogram) can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to dose modification or study drug discontinuation or meets any serious criteria). If this is the case, it must be recorded in the source document and as an AE on the appropriate AE page of the eCRF. The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- **SAE Mailbox:** PPD
- **SAE Hotline (USA and Canada):** PPD
- **SAE Fax line (USA and Canada):** PPD

8.6.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include pre-listed AEs (solicited ARs) and intensity scales. In addition to the eDiaries, delegated site staff will interview the participant to assess the occurrence of any unsolicited AEs, SAEs, and medications taken. The investigator or designated site staff will transcribe the collected information into the eCRF.

The investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to the IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.6.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All AEs and SAEs (as defined in Appendix 2) will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 2.

8.6.4. Adverse Events of Special Interest

The definition of AESIs and reporting of AESIs is presented in Section 11.2.5 and Section 11.2.12 (Appendix 2), respectively. Adverse events of special interest for this protocol, including myocarditis/pericarditis and anaphylaxis, among others, are listed in Section 11.2.13 (Appendix 2). For Centers for Disease Control and Prevention (CDC) working case definitions of myocarditis, pericarditis, and myopericarditis occurring after receipt of COVID-19 mRNA vaccines, refer to Section 11.4 (Appendix 4).

8.6.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IP under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE/AESI or other specific safety information (eg, summary or listing of SAEs/AESIs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8.6.6. Pregnancy

Details of all pregnancies occurring in female participants after the administration of IP must be reported to the Sponsor or designee within 72 hours of learning of the pregnancy following the procedures outlined in Appendix 2. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Further information on the collection of pregnancy information is given in Appendix 2.

8.7. Treatment of Overdose

In the event of an overdose, the investigator should do the following:

1. Contact the Medical Monitor SAE hotline immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until the last safety follow-up visit.
3. Report any signs or symptoms associated with the overdose as an AE and record details in the relevant AE/SAE sections in the eCRF.
4. Document the quantity of the excess dose in the eCRF.

8.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.10. Biomarkers

Analysis of biomarkers for biological activity will include the evaluation of the ZIKV-specific antibody response, such as nAbs and bAbs, and additionally relevant immunological variables (Section 8.3), which may correlate with vaccine efficacy.

8.11. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study objectives are presented in Section 3.

There is no hypothesis testing in this study.

9.2. Sample Size Determination

The sample size for this study is not driven by statistical assumptions for formal hypothesis testing. This sample size is regarded as sufficient to provide an understanding of the safety profile of mRNA-1893 and to confirm the dose selection to advance development into future studies.

Approximately 800 participants will be randomly assigned in a 1:1:1:1 ratio to receive 2 doses of CCI µg mRNA-1893 separated by 28 days (Treatment Arm A), 2 doses of CCI µg mRNA-1893 separated by 28 days (Treatment Arm B), a single dose of CCI µg mRNA-1893 on Day 29 following a single dose of placebo on Day 1 (Treatment Arm C), or 2 doses of placebo separated by 28 days (Treatment Arm D). A total of 600 participants will receive mRNA-1893, 200 participants in each dosing arm, with approximately 100 participants in each flavivirus serostatus cohort and dosing arm; approximately 200 participants will receive placebo. Table 11 presents the 95% confidence interval (CI) for 1 participant with an AE and the lowest AE rate detectable with at least 95% probability for each selected sample size. The 2-sided 95% CI was calculated using the Clopper-Pearson method for one proportion in SAS 9.4 software. A sample size of 200 (or 400) has at least a 95% probability to observe at least 1 participant with an AE at a true 1.49% (or 0.75%) AE rate.

Table 11: 95% Confidence Interval for One Participant with an Adverse Event and the Lowest Detectable Incidence Rate at 95% Probability in Each Selected Sample Size

Sample Size Receiving mRNA-1893	Rate and 95% CI (%) at One Participant with AE			Lowest Detectable Rate (%) with ≥ 95% Probability
	AE Rate	Lower CI	Upper CI	
100	1.00	0.03	5.45	2.95
200	0.50	0.01	2.75	1.49
400	0.25	0.01	1.38	0.75
600	0.17	0.00	0.93	0.5

Abbreviations: AE = adverse event; CI = confidence interval.

For the comparison of immunogenicity, the sample size will provide adequate statistical power (approximately 90%) to detect a large effect size (4-fold or above in ZIKV-specific nAb titers, as measured by PRNT50 at Day 57) under reasonable assumptions.

9.3. Populations for Analyses

9.3.1. Randomized Set

The Randomized Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. Participants will be included in the treatment arm to which they are randomized.

9.3.2. Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomly assigned and received any IP and contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the treatment arm corresponding to the IP they actually received.

9.3.3. Safety Set

The Safety Set consists of all participants who are randomly assigned and received any IP. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the treatment arm corresponding to the IP they actually received for the analysis of safety data using the Safety Set.

9.3.4. Full Analysis Set

The Full Analysis Set (FAS) consists of all participants who are randomly assigned and a) received any IP, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least 1 post-IP injection assessment for the analysis endpoints as specified in b). Participants will be included in the treatment arm to which they are randomly assigned.

9.3.5. Per-Protocol Set

The PP set consists of all FAS participants who a) comply with the vaccination schedule, b) comply with the timings of immunogenicity blood sampling to have post-IP injection results available for at least 1 assay component corresponding to the immunogenicity analysis objective, and c) have no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective.

The PP set will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be included in the treatment arm to which they are randomly assigned.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and treatment unblinding and will describe the analysis populations to be included in the analyses along

with missing handling. Analysis of exploratory endpoints will also be described in the SAP as appropriate. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Baseline Descriptive Statistics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by treatment arm overall (regardless of baseline serostatus) and by baseline flavivirus status assessed by dengue and West Nile specific serologies and treatment arm using descriptive statistics (mean, median, minimum, maximum, and standard deviation for continuous variable, and number and percentage for categorical variables).

The treatment arms are:

- mRNA-1893: 2 doses of CCI µg, separated by 28 days.
- mRNA-1893: 2 doses CCI µg, separated by 28 days.
- mRNA-1893: CCI µg, 1 dose on Day 29 (1 dose of placebo on Day 1).
- Placebo: 2 doses of placebo, separated by 28 days.

9.4.2. Efficacy Analyses

Not applicable.

9.4.3. Safety Analyses

Safety analyses will include solicited ARs (local and systemic), unsolicited AEs, SAEs, AESIs, MAAEs, and AEs leading to vaccine/study withdrawal, and vital sign measurements.

The intensity of solicited ARs, unsolicited AEs, and vital sign measurements will be graded as described in Section 11.2.8 (Appendix 2).

All safety analyses will be based on the Safety Set, except analyses of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment arm overall (regardless of serostatus) and by baseline flavivirus status assessed by dengue and West Nile specific serologies, and vaccination (first, second), unless otherwise specified.

Solicited local and systemic ARs during the 7-day follow-up period after each IP injection will be tabulated by number and percentage of participants reporting ≥ 1 event. The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each IP injection will be provided with a 2-sided 95% exact CI using the Clopper-Pearson method.

Unsolicited AEs will be coded according to the Medical Dictionary for Regulatory Activities (Dictionary for Adverse Reaction Terminology version). Unsolicited AEs, treatment-related AEs, SAEs, AESIs, MAAEs, and AEs leading to discontinuation from IP or participation in the study, severe AEs, and deaths will be reported by number and percentage of participants reporting ≥ 1 event, and number of events. Table 12 summarizes analysis strategy for solicited AR and unsolicited AE parameters.

Table 12: Analysis Strategy for Solicited Adverse Reactions and Unsolicited Adverse Events Parameters

Safety Endpoint	Descriptive Statistics (Number and Percentage of Participants)[1]	95% CI[2]
Any solicited AR	X	X
Any unsolicited AE	X	
Any unsolicited treatment-related AE	X	
Any SAE	X	
Any AESI	X	
Any treatment-related SAE	X	
Any unsolicited MAAE	X	
Any unsolicited treatment-related MAAE	X	
Any unsolicited AE leading to discontinuation from IP	X	
Any unsolicited AE leading to discontinuation from participation in the study	X	
Any severe unsolicited AE	X	
Any severe unsolicited treatment-related AE	X	
Any fatal AE	X	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; CI = confidence interval; IP = investigational product; MAAE = medically attended adverse event; SAE = serious adverse event.

[1] X = results will be provided.

[2] 95% CI using the Clopper-Pearson method.

For all other safety parameters, descriptive summary statistics will be provided.

Further details will be described in the SAP.

9.4.4. Immunogenicity Analyses

Immunogenicity analyses will be conducted on the PP set, reported by treatment arm overall and by baseline flavivirus status assessed by dengue and West Nile specific serologies as applicable.

If the number of participants in the FAS and PP set differ by more than 10%, supportive immunogenicity analyses may be conducted on the FAS.

For the primary and secondary immunogenicity endpoints, descriptive summary statistics of antibody-mediated immunogenicity at each time point will include GMT (for nAbs), median, minimum, maximum, 95% CI, and geometric mean fold rise of post-baseline/baseline nAb titers with corresponding 95% CI.

For GMT calculations, antibody titers reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with seroconversion will be provided with 2-sided 95% CI using Clopper-Pearson method by treatment arm overall and by baseline flavivirus serostatus.

The number and percentage of participants with seroresponse will be provided with 2-sided 95% CI using Clopper-Pearson method by treatment arm in baseline flavivirus-seronegative participants.

The number and percentage of participants with ≥ 2 or ≥ 4-fold rise in ZIKV-specific nAb titers will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint.

Seroconversion is defined as either an increase in ZIKV-specific nAb titer from below the LLOQ to a titer equal to or above LLOQ, or an increase of at least 4 fold in ZIKV-specific nAb titer in participants with pre-existing nAb titers, as measured by a specific assay/methodology.

Seroresponse is defined as an increase in ZIKV-specific nAb titer from below the LLOQ to greater than or equal to the LLOQ, as measured by a specific assay/methodology.

Further details will be described in the SAP.

9.5. Study Planned Analyses

The following analyses will be conducted on cleaned data:

1. An IA of safety and immunogenicity data will be performed after all participants have completed Day 57 (28 days after the IP injection). The Day 57 IA will be performed by a separate team of unblinded programmers and statisticians. Pre-identified Sponsor team members will be unblinded to review treatment level results, as defined in the study Data Blinding Plan. The unblinded statistics team will not be involved in either study design or the regular study conduct. The participants and study sites will remain blinded until the

conclusion of the study. The IA will serve as the basis for the progression to the ZIKV Phase 3 studies.

2. The final CSR will include full unblinded analyses of all safety and immunogenicity with individual unblinded listings through Day 196 (all data through approximately 6 months after the last IP injection).
3. An addendum to the CSR will include the safety and immunogenicity data from Month 8 until EOS for all participants enrolled in the Extension Period.

More details can be found in the SAP.

In addition, unblinded data presentation or analysis for DSMB review will be handled by the unblinded team of statisticians and programmers, who are not involved in study design. More details regarding DSMB analysis can be found in the DSMB Charter.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. APPENDIX 1: Study Governance Considerations

11.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Union regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

11.1.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site to:

- Determine the adequacy of the facilities.

- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor, designated CRO, and the investigator.

According to ICH GCP guideline, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded in the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB/IEC review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the Clinical Monitoring Plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs/AESIs have been properly documented in eCRFs and confirm any SAEs/AESIs have been forwarded to the SAE Hotline, and those SAEs/AESIs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

11.1.3. Audits and Inspections

The Sponsor, their designee(s), the IRB/IEC, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IRB/IEC, or regulatory authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6(R2), and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

11.1.4. Financial Disclosure

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 the Sponsor with 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.

The Sponsor, the CRO, and the study site are not financially responsible for further testing or treatment of any medical condition that may be detected during the eligibility evaluation. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

11.1.5. Recruitment Procedures

Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB.

11.1.6. Informed Consent Process

The informed consent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center. All consent documents will be approved by the appropriate IRB/IEC. The actual ICF used at each center may differ, depending on local regulations and IEC/IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC/IRB prior to the form being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him/her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. Participants must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

Participants must be allowed sufficient time to decide whether they wish to participate.

The participant must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB/IEC, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant should also be informed that he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow

any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

At Visit 10 (Day 196), all participants will have the opportunity to provide their consent to participate in the Extension Period (through Day 700).

11.1.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s)/IEC(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by the Sponsor, agreed by the investigator(s), and approved by the relevant IRB(s)/IEC(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the ICF have been approved by relevant IRB(s)/IEC(s) must be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigator(s), and notified to the IRB(s)/IEC(s).

11.1.8. Protocol Violations and Deviations

The investigator or designee must document and explain in the participant'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 participants 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 participants or a small group of participants and do not

involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when the participant or investigator does not adhere to the protocol, resulting in a significant additional risk to the participant. Protocol violations can include nonadherence to inclusion or exclusion criteria, enrollment of the participant without prior Sponsor approval, or nonadherence to FDA regulations or ICH E6(R2) 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.

11.1.9. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant will be asked to complete a form allowing the investigator to notify the participant's primary healthcare provider of his/her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant 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 participant, 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 confidential information to other parties.

11.1.10. Sample Retention and Future Biomedical Research

Samples may be used for purposes related to ZIKV research, in particular assay development, assay validation, and animal challenge studies. There will be no human genetic testing (whole genome sequencing or creation of cell lines) performed on these samples. The DNA of the CMI subset participants may be used to further characterize the immune response to mRNA-1893 vaccine, but only epitopes relevant to the ZIKV-specific immune response will be investigated. The samples may be stored for 20 years or until the study team has determined that specimens are no longer needed, per local requirements. In addition, identifiable samples can be destroyed at any time at the request of the participant.

11.1.11. Study Safety Oversight by Oversight Safety Team and Data Safety Monitoring Board

Study safety will be monitored by an OST that will include the investigators participating in the study and the protocol team, which will include the CRO Medical Monitor and the Sponsor Clinical Development Physician and may include additional representatives from the Sponsor Project Team. The CRO Medical Monitor will be responsible for performing a review of the enrollment and study-related safety data with oversight by the Sponsor Clinical Development Physician. During the Vaccination Period, a formal biweekly meeting/teleconference will be scheduled among the CRO Medical Monitor, the Sponsor Clinical Development Physician, and the Lead Investigator (or alternate investigator) to review safety events in a blinded fashion. Once all participants in all treatment arms enter the Follow-Up Period, the interval of these meetings may be extended to monthly. This decision will be confirmed by the protocol team.

In addition, an independent DSMB will be established for Study mRNA-1893-P201. It will be composed of experts with experience in clinical development and vaccines and with expertise in flaviviruses. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will convene on an approximately quarterly basis until study end. Additionally, the DSMB may convene at any time if there is an ad-hoc safety concern detected by the protocol team. This independent board will be informed of the progress and conduct of the study; their primary responsibility will be to review unblinded study data to evaluate the safety findings. All AEs, SAEs, AESIs, and MAAEs will be reviewed by the board, and they will be asked to provide recommendations and guidance as to management of safety follow-up within the study. In addition, should immunogenicity findings request further opinion, the DSMB would be asked to review unblinded available immunogenicity data and provide guidance.

Details regarding the composition, responsibilities, and procedures of the OST and the DSMB will be presented in the OST and DSMB charters, respectively.

11.1.12. Dissemination of Clinical Study Data

The Sponsor shares information about clinical studies and results on publicly accessible websites, based on international and local legal and regulatory requirements, and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, European Union clinical trial register (eu.ctr), etc., as well as some national registries.

In addition, results from clinical studies are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available the privacy of participants in clinical studies sponsored by the Sponsor is assured. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

11.1.13. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that

the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance (QA) includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A QA representative from the Sponsor or its qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

11.1.14. Data Collection and Management

This study will be conducted in compliance with the ICH document "Guidance for Industry-E6 (R2) Good Clinical Practice: Consolidated Guidance," dated November 2016. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the investigational site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities. Concomitant medications will be coded using the WHO – Drug Reference List.

11.1.15. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, ICFs, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the paper case report form or entered into the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts and the signed ICFs are to be included in the investigator's files with the participant's study records.

11.1.16. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation.] If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

11.1.17. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Continuation of the study represents a significant medical risk to participants.
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further mRNA-1893 development.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

11.1.18. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

11.2. APPENDIX 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

11.2.1. Definition of an AE

AE Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, regardless of whether it is considered drug related. • A treatment-emergent AE is defined as any event not present before exposure to the IP or any event already present that worsens in intensity or frequency after exposure to the IP. An AR is any AE for which there is a reasonable possibility that the IP caused the AE (Section 11.2.3). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the IP and the AE. An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR in the protocol but starts outside the protocol-defined post-injection period for reporting solicited ARs (ie, for the 7 days after each IP injection).

Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after the first dose of IP even though they may have been present before the start of the study.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

11.2.2. Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An AE is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32(a)):

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, regardless of whether it is considered IP related.

b. Is life-threatening

An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that might have caused death if it had occurred in a more severe form.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization indicates that the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during hospitalization will be recorded as AEs; however, if a complication/AE prolongs hospitalization or otherwise fulfills the SAE criteria, the complication/AE will be recorded as a separate SAE.

d. Results in significant incapacity disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a medically important event:

- Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the Sponsor as described in Section 8.6.

11.2.3. Definition of Solicited Adverse Reactions

The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-IP injection period (day of injection and 6 subsequent days), using a pre-defined checklist in the eDiary (ie, solicited ARs; Section 8.5.1).

The following local (injection site) ARs will be solicited: pain, erythema (redness), swelling/induration (hardness).

The following systemic ARs will be solicited: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, body temperature (potentially fever), and chills.

The study site staff will contact the participant within 24 hours of becoming aware of the event in case a severe (Grade 3) local or systemic AR occurs within 7 days after IP injection.

The investigator will review, confirm, and grade reactogenicity according to the grading scales presented in Table 13 (Section 11.2.8), Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond 7 days after an injection, the participant will be prompted to capture the solicited local or systemic AR in the eDiary until it is no longer reported, not to exceed 28 days after each injection (Section 8.5.1). Solicited adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call (Section 8.5.2) or at the following study visit.

All solicited local ARs will be considered causally related to vaccination.

Note: Any solicited AR that meets any of the following criteria must be entered into the participants' source document and must also be recorded by the study site on the Reactogenicity page of the participant's eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (MAAE; Section 11.2.4).
- Solicited local or systemic AR that leads to the participant withdrawing from the study or the participant being withdrawn from the study by the Investigator (AE leading to withdrawal).
- Solicited local or systemic AR lasting beyond 7 days after an injection.

- Solicited local or systemic AR that leads to participant withdrawal from IP.
- Solicited local or systemic AR that otherwise meets the definition of an SAE (Section 11.2.2).
- Solicited AR with a toxicity score of Grade 3 or greater.

11.2.4. Definition of Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner. This would include visits to study site for unscheduled assessments and visits to healthcare practitioners external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs (ie, MAAEs) will be captured on the AE page of the eCRF.

11.2.5. Definition of Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor are required. Such events may require further investigation to characterize and understand them. Adverse events of special interest for this protocol are listed in Section 11.2.13 (Appendix 2).

11.2.6. Recording and Follow-Up of an AE and/or SAE

The participants will be instructed to contact the investigator immediately should they develop any untoward signs or symptoms or any medical condition that leads to hospitalization or an emergency room visit. In addition, the study site staff will contact the participant within 24 hours of becoming aware of the event if any of the following is reported via eDiary within 7 days after IP injection: severe (Grade 3) local or systemic ARs (Table 13).

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the eCRF in standard medical terminology, along with the date and time of onset and the date and time of resolution.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the AE/SAE page of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant

number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.

The investigator will attempt to establish a single diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to mRNA-1893.

11.2.7. Pregnancy

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 72 hours of the site learning of its occurrence (Section 11.3.3). If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of the safety follow-up for the study has ended. 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 pregnancy resulting in an abnormal outcome according to the procedures described for SAEs (Section 11.2.11).

11.2.8. Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007), presented in Table 13 will be used to record the intensity of solicited ARs and vital sign measurements observed during this study.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Changes in the severity of an AE should be documented in the participant's source documentation 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. An

AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

Table 13: Toxicity Grading

Local Reaction to Injectable Product	**None (Grade 0)**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4[a])**
Pain at injection site	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	ER visit or hospitalization
Injection site Erythema/Redness*	<2.5 cm	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Injection site Induration/Swelling**	<2.5 cm	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

[a] Grading for Grade 4 events per investigator assessment (with the exception of fever).
Abbreviation: AE = adverse event; eCRF = electronic case report form; ER = emergency room.
Note: Events listed above but starting > 7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the investigator.
* 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 Preventive Vaccine Clinical Trials; Tables for Clinical Abnormalities (DHHS 2007).

Systemic (General)	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4[a])
Fever (°C)* (°F)*	< 38.0°C < 100.4°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	None	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
Chills	None	No interference with activity	Some interference with activity not requiring medical attention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

[a] Grading for Grade 4 events per investigator assessment (with exception of fever).
Abbreviations: AE = adverse event; eCRF = electronic case report form; ER = emergency room; IV = intravenous.
Note: Events listed above but starting > 7 days post study injection will be recorded on the AE page of the eCRF. Causality for each event will be determined per assessment by the investigator.
* 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 Preventive Vaccine Clinical Trials; Tables for Clinical Abnormalities (DHHS 2007). Division of AIDS Grading the Severity of Adult and Pediatric Adverse Events (DHHS 2014).

Table 14: Table for Clinical Abnormalities

Vital Sign*	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.
* Participant 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 participant populations, for example, conditioned athletes.
Source: Guidance for Industry – Toxicity Grading Scale for Heathy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; Tables for Clinical Abnormalities (DHHS 2007).

11.2.9. Assessment of Causality

Assessment of Causality

All solicited injection site ARs are considered to be related to IP.

The investigator's assessment of an AE's relationship to the IP is part of the documentation process but is not a factor in determining what is or is not reported in the study. The causality assessment between the solicited systemic ARs/unsolicited AEs and mRNA-1893 exposure is one of the criteria used when determining regulatory reporting requirements. For each solicited systemic AR/unsolicited AE, the investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) according to the categories below:

Not Related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP, or temporal sequence of the AE onset relative to administration of the IP is not reasonable, or the AE is more likely explained by another cause than the IP.

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

Assessment of Expectedness

- An AE or solicited AR is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed with the vaccine being tested or, if an IB is not required or available, it 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 IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected ARs that are mentioned in the IB 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.

11.2.10. Follow-Up of AEs and SAEs

Follow-Up of AEs and SAEs

- All AEs, SAEs, and MAAEs must be reported in detail on the appropriate page of the eCRF and followed until the event is resolved or stable or judged by the investigator to be not clinically significant.

11.2.11. Reporting of SAEs

Any AE considered serious by the investigator or that meets SAE criteria (Section 11.2.2) 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 IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 CFR Parts 312 and 320. The investigator is responsible for notifying the IRB directly.

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours of becoming aware of the event.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or using the following contact information:
  - **SAE Mailbox:** PPD
  - **SAE Hotline (USA and Canada):** PPD

SAE Reporting to the Sponsor or Designee via Paper Case Report Form

- A backup plan is used (using a paper SAE form) when the eCRF system does not work and should be faxed to the Sponsor at:
  - **SAE Fax line (USA and Canada):** PPD
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE case report form pages within the designated reporting time frames.

11.2.12. Reporting of AESIs

The process for reporting an AESI ensures compliance with 21 CFR 312 and ICH GCP guidelines.

All AESIs will be collected through the entire study period and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system. If a site receives a report of a new AESI from a participant or receives updated information on a previously reported AESI at a time after the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox. After learning that a participant has experienced an AESI, the Investigator or designee is responsible for reporting the AESI to the Sponsor, regardless of relationship or expectedness. If the AESI meets the criteria for an SAE, the SAE reporting procedure should be followed.

11.2.13. Adverse Events of Special Interest Terms

Investigators should report all events that fall into the categories presented in Table 15 as an AESI per the reporting processes in Section 11.2.12. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines.

Table 15: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts < 150×10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome
New onset of or worsening of the following neurologic diseases:	• Guillain-Barré Syndrome • Acute disseminated encephalomyelitis (ADEM) • Idiopathic peripheral facial nerve palsy (Bell's palsy) • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions

Medical Concept	Additional Notes
Anaphylaxis	• Anaphylaxis as defined per Section 11.2.13.2 • Follow reporting procedures in Section 11.2.12
Myocarditis/Pericarditis	• Myocarditis • Pericarditis • Myopericarditis • Refer to Section 11.2.13.1 for details.

11.2.13.1. Myocarditis/Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets seriousness criteria (Section 11.2.2). The CDC case definition is provided in Section 11.4 (Appendix 4) as guidance.

11.2.13.2. Anaphylaxis

All suspected cases of anaphylaxis should be recorded as an AESI and reported as an SAE, based on the criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, per Section 11.2.11. The Investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs or symptoms consistent with anaphylaxis (as described below) should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources.

Anaphylaxis is a clinical syndrome characterized by the following:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involves 2 or more organ systems, as follows:

- **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes.
- **Cardiovascular:** measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation.
- **Respiratory:** bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea.
- **Gastrointestinal:** diarrhea, abdominal pain, nausea, vomiting.

11.3. APPENDIX 3: Contraceptive Guidance and Collection of Pregnancy Information

11.3.1. Definitions: Women of Childbearing Potential

Females of childbearing potential are those who are considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of mRNA-1893, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential:

1. Premenarchal.
2. Premenopausal, surgically sterile female with one of the following:
    a. Documented complete hysterectomy.
    b. Documented bilateral salpingectomy.
    c. Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women < 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and FSH levels in the postmenopausal range for the institution.
    - Women ≥ 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal

replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

11.3.2. Contraception Guidance:

Female participants must be nonpregnant and nonlactating and meet one of the following criteria:

a. Postmenopausal (defined as amenorrhea for 12 consecutive months without an alternative medical cause or documented serum FSH level in the postmenopausal range);
b. Surgically sterile (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).

NOTE: Procedures and laboratory results must be confirmed in the medical record, by physical examination, or by official written confirmation of a procedure; or

c. If of childbearing potential, has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first vaccination (Day 1) and agrees to consistently use a highly effective (ie, < 1% failure rate per year) method of contraception (Table 16) through 3 months after the last IP injection. Female participants should also refrain from breastfeeding throughout this period.

Table 16: Highly Effective Methods of Contraception (< 1% Failure Rate)

Barrier/Intrauterine Methods	Hormonal Methods
Copper T intrauterine device Levonorgestrel-releasing intrauterine system (eg, Mirena®)[1]	Implants: Etonogestrel-releasing implants (eg, Implanon®) or levonorgestrel-releasing implant (eg, Norplant®) Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing® Injection: Medroxyprogesterone injection: eg, Depo-Provera® Combined Pill: Normal and low dose combined oral contraceptive pill Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra® Mini pill: Progesterone-based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[1] This is also considered a hormonal method.

11.3.3. Collection of Pregnancy Information

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the site learning of its occurrence.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 72 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality). The investigator will collect follow-up information on the participant and the child, even if the participant is discontinued from the study, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Spontaneous miscarriages, congenital anomaly, and/or birth defect abortion should be reported as SAEs.

- Any post-study, pregnancy-related SAE considered reasonably related to the mRNA-1893 by the investigator will be reported to the Sponsor as described in Section 7.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue mRNA-1893 or be withdrawn from the study.

11.4. APPENDIX 4: CDC Working Case Definitions of Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

Table 17: Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute Myocarditis	**Probable Case**	**Confirmed Case**
	Presence of ≥ 1 new or worsening of the following clinical symptoms:* • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR**, infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥ 1 new finding of • troponin level above upper limit of normal (any type of troponin) • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis§ • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis¶ **AND** • No other identifiable cause of the symptoms and findings	Presence of ≥ 1 new or worsening of the following clinical symptoms:* • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope **OR,** infants and children aged < 12 years might instead have ≥ 2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy **AND** ≥ 1 new finding of • histopathologic confirmation of myocarditis† • cMRI findings consistent with myocarditis¶ in the presence of troponin level above upper limit of normal (any type of troponin) **AND** • No other identifiable cause of the symptoms and findings

Condition	Definition
Acute Pericarditis**	Presence of ≥ 2 new or worsening of the following clinical features: • acute chest pain†† • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG or EKG = electrocardiogram; MRI = magnetic resonance imaging.

Note: An independent Cardiac Event Adjudication Committee (CEAC) comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet Center for Disease Control and Prevention criteria for "probable" or "confirmed" events, (Gargano et al 2021), and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

† Using the Dallas criteria (Aretz et al 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

¶ Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihubexternal icon

** https://academic.oup.com/eurheartj/article/36/42/2921/2293375external icon

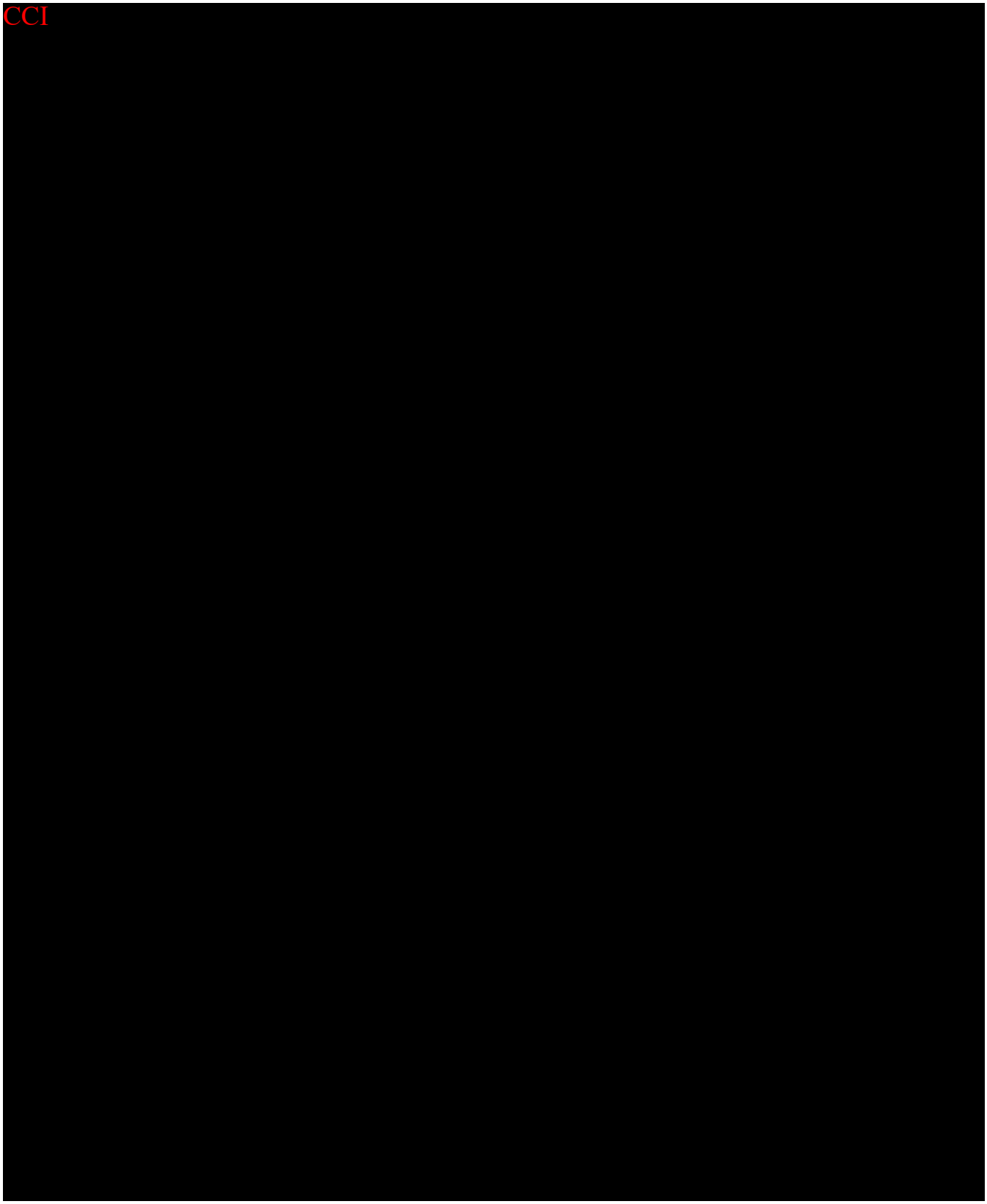
†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Reference: (Gargano et al 2021).

11.5. APPENDIX 5: Protocol Amendment History

11.5.1. Amendment 2 (27 Oct 2021)

11.5.2. Amendment 1 (16 Sep 2021)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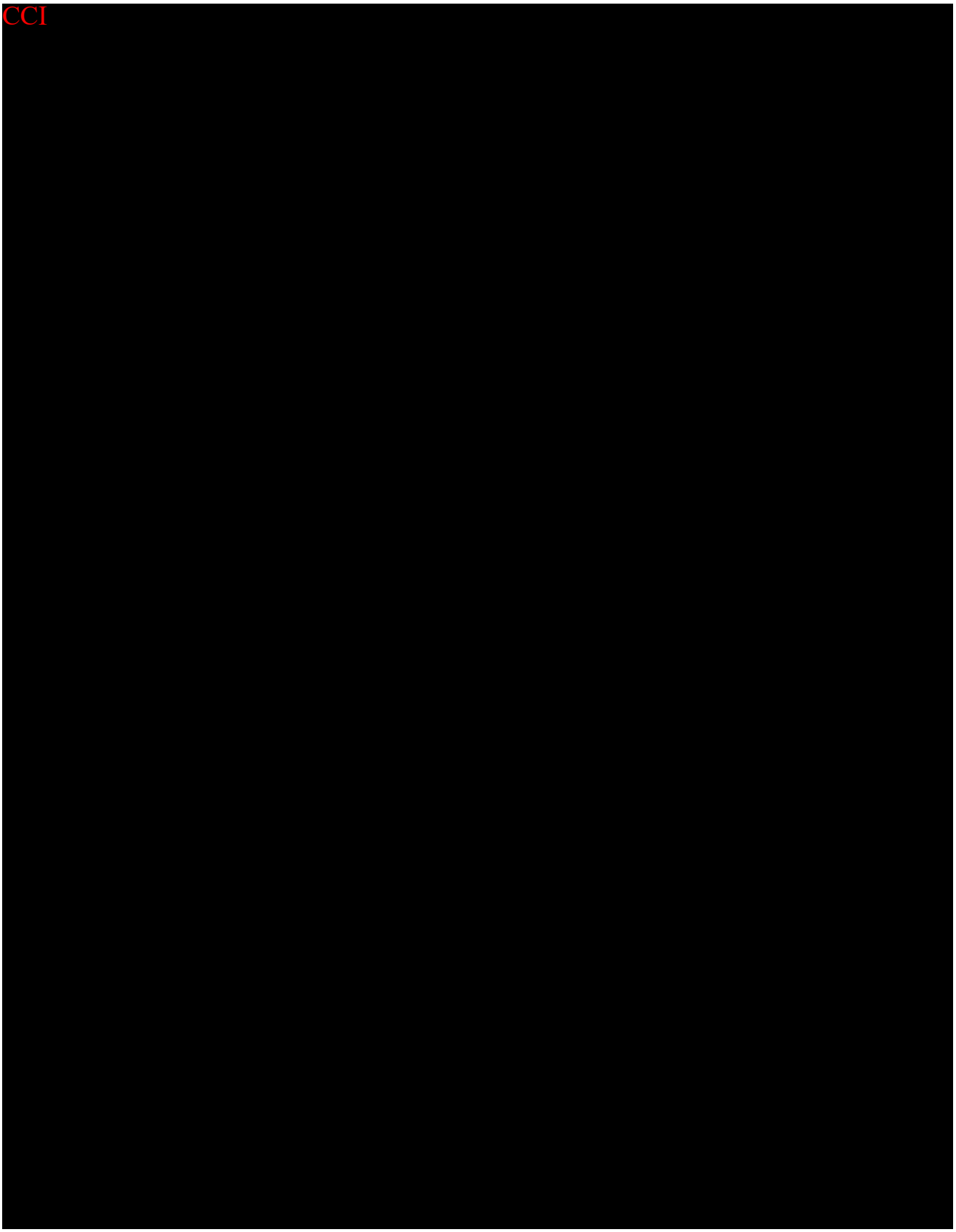
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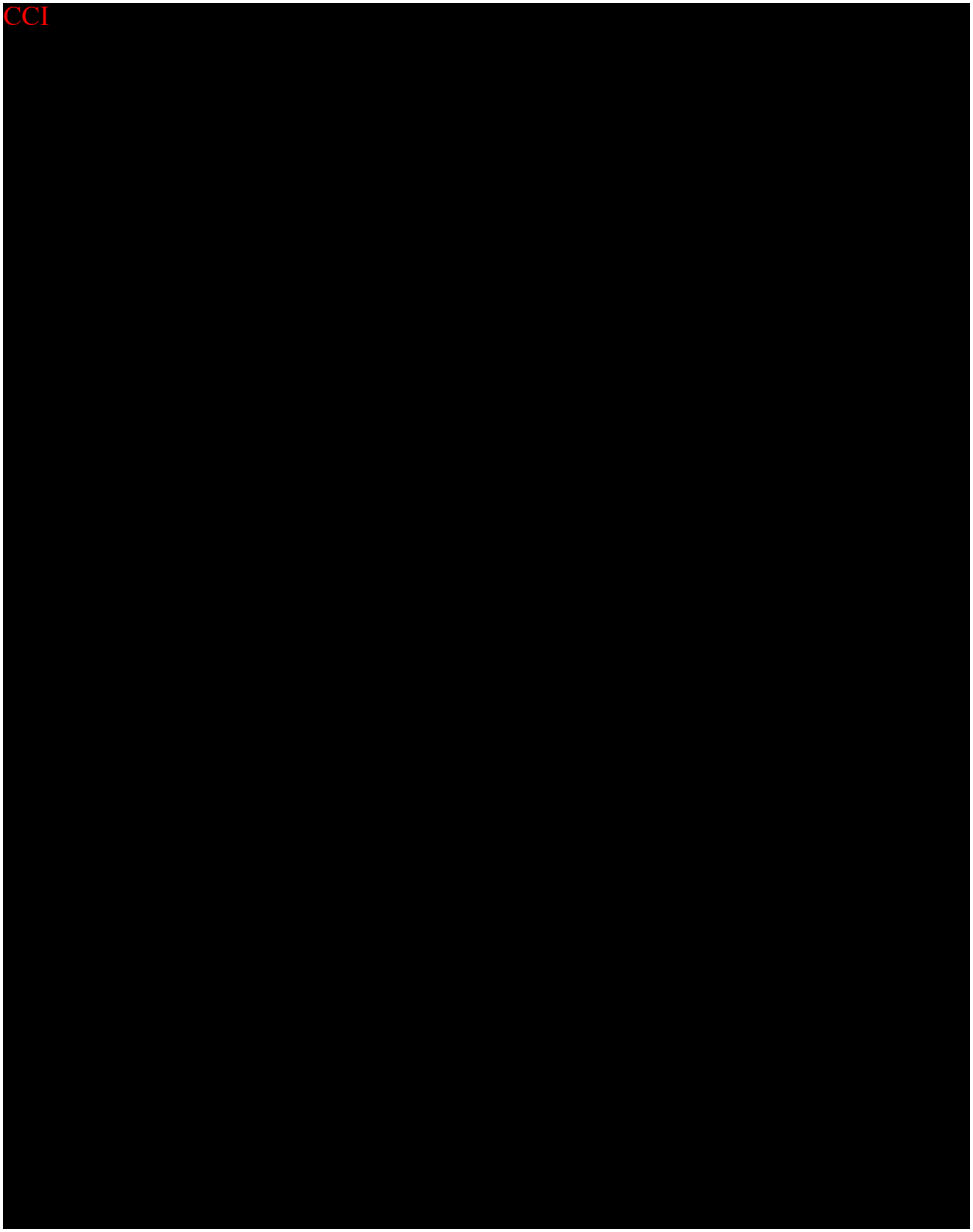


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