ModernaTX, Inc.

mRNA-1893-P101

A Phase 1, Randomized, Observer-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Tolerability, and Immunogenicity of Zika Vaccine mRNA-1893 in Healthy Flavivirus Seropositive and Seronegative Adults

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Statistical Analysis Plan

Version 3.0

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Document History

Version	Date	Changes
1.0	24Oct2019	Original Version
2.0	18Mar2020	Removed references to 1:10 for the LLOQ in Section 4.2, and Section 4.3
3.0	20 May 2021	Visit window for Immunogenicity for month 13 changed to [343, 385] Changed GMT to GMC Changed of "bAb titer from below the LLOQ" to "a change of bAb concentration from below the LLOQ" Changed "2-fold or 4-fold increase in bAb titers" to "2-fold or 4-fold increase in bAb concentration

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
bAb	serum binding antibody
BMI	body mass index
CI	confidence interval
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
GMT	geometric mean titer
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	Internal Review Board
IRT	Interactive Response Technology
IST	Internal safety team
ITT	intent-to-treat
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization assay
nAb	serum neutralizing antibody
PP	per-protocol
PRNT	plaque reduction neutralization test

Abbreviation	Definition
PT	preferred term
RVNT	reporter virus neutralization test
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
ZIKV	Zika virus

1 Administrative Structure

This study is being conducted under the sponsorship of ModernaTX, Inc. The safety and immunogenicity statistical analyses are being performed under contract with PPD in collaboration with ModernaTX, Inc.

2 Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1893-P101, is based on the most recent approved clinical study protocol, Version 2.0, dated 17 July 2019 and the most recent approved electronic case report form (eCRF) Version 5.0, dated 24 July 2019.

In addition to the information presented in the statistical analysis plans section of the protocol (Section 3.6) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and information that was not available at the time of protocol finalization.

PPD Biostatistics and Programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and immunogenicity data; Statistical Analysis System (SAS; Version 9.4 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

The SAP will be finalized and approved prior to the first interim analysis clinical database lock and treatment unblinding for the study. If the statistical analysis methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

3 Study Objectives

3.1 Primary Objective

The primary objective of the study is to evaluate the safety, tolerability, and reactogenicity of a 2-dose vaccination schedule of mRNA-1893 Zika vaccine, given 28 days apart, across a range of dose levels in flavivirus-seronegative and flavivirus-seropositive participants compared with placebo.

3.2 Secondary Objective

The secondary objective of the study is to evaluate the immunogenicity of a 2-dose vaccination schedule of mRNA-1893 Zika vaccine, given 28 days apart as measured by Zika virus (ZIKV)-specific neutralization assay (Plaque Reduction Neutralization Test [PRNT]).

3.3 Exploratory Objectives

The exploratory objectives of the study are the following:

1. To evaluate the immunogenicity of a 2-dose vaccination schedule of mRNA-1893 Zika vaccine, given 28 days apart, as measured by enzyme-linked immunoabsorbent assay (ELISA) and additional neutralization assays.
2. To assess the occurrence of flavivirus infection throughout the course of participation in the trial.

4 Study Endpoints

4.1 Primary Endpoints

The primary endpoints for the study are the following:

- Frequency and grade of each solicited local and systemic reactogenicity adverse reaction (AR) during a 7-day follow-up period after each vaccination
- Frequency and grade of any unsolicited adverse events (AEs) during the 28-day follow-up period after each vaccination
- Frequency of any medically attended adverse event (MAAE), serious adverse event (SAE), and adverse event of special interest (AESI) from Day 1 to the end of study (EOS) Visit at Month 13

Other safety assessments include clinical laboratory test results (hematology, serum chemistry, and coagulation); vital sign measurements; and physical examination findings.

4.2 Secondary Endpoints

The secondary endpoints for the study are the following:

- Geometric mean titer (GMT) of neutralizing antibody (nAb) against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT

- GMT of nAb in initially seronegative participants against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT
- GMT of nAb in initially seropositive participants against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT
- Percentage of participants who seroconverted from Day 1 (baseline) to Day 29, from Day 1 to Day 57, from Day 1 to Month 7, and from Day 1 to Month 13. A seroconversion is defined as a change of PRNT from below the lower limit of quantification (LLOQ) to a PRNT equal to or above LLOQ, or an increase of at least 4-foldin participants with pre-existing PRNT titers.
- Proportion of initially seronegative participants with a seroresponse at Day 29, Day 57, Month 7, and Month 13 as measured by PRNT. A seroresponse is defined as a change of PRNT from below the LLOQ to greater than or equal to the LLOQ.
- Proportion of initially seropositive participants with a 2-fold or 4-fold increase in nAb titers as compared with baseline as measured by PRNT

4.3 Exploratory Endpoints

The exploratory endpoints for the study include the following:

- GMT of nAb against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by additional neutralization assay
- GMT of nAb in initially seronegative participants against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by additional neutralization assay
- GMT of nAb in initially seropositive participants against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by additional neutralization assay
- Percentage of participants who seroconverted from Day 1 (baseline) to Day 29, from Day 1 to Day 57, from Day 1 to Month 7, and from Day 1 to Month 13. A seroconversion is defined as a change of nAb titer (by additional neutralization assay) from below the LLOQ to a titer equal to or above LLOQ, or a multiplication by at least 4 in participants with pre-existing nAb titer as measured by additional neutralization assay
- Proportion of initially seronegative participants with a seroresponse at Day 29, Day 57, Month 7, and Month 13 as measured by additional neutralization assay. A

seroresponse is defined as a change of titer from below the LLOQ to greater than or equal to the LLOQ.

- Proportion of initially seropositive participants with a 2-fold or 4-fold increase in nAb titers as compared with baseline as measured by additional neutralization assay
- GMC of serum binding antibodies (bAb) against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay
- GMC of bAb in initially seronegative participants against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay
- GMC of bAb in initially seropositive participants against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay
- Percentage of participants who seroconverted from Day 1 (baseline) to Day 29, from Day 1 to Day 57, from Day 1 to Month 7, and from Day 1 to Month 13. A seroconversion is defined as a change of bAb concentration from below the LLOQ to a titer equal to or above the LLOQ, or a multiplication by at least 4 in participants with pre-existing bAb concentration as measured by ELISA binding assay
- Proportion of initially seronegative participants with a seroresponse at Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay
- Proportion of initially seropositive participants with a 2-fold or 4-fold increase in bAb concentration as compared with baseline as measured by ELISA binding assay
- Immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against envelope- and NS1- based antigens present in serum collected at baseline and at end of study measured as antibody binding by ELISA or equivalent methodology to flaviviruses

5 Study Design

5.1 Overall Study Design

This is a Phase 1, randomized, observer-blind, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of Zika vaccine mRNA-1893 administered to healthy flavivirus-seropositive and seronegative adult participants (18 to

49 years of age, inclusive). A total of 120 participants (30 participants per cohort) will be enrolled into 1 of 4 mRNA-1893 dose cohorts (10, 30, 100, or 250 µg). Within each cohort, eligible participants will be randomly assigned to mRNA-1893 or placebo (4:1 mRNA-1893 to placebo) and administered the study vaccine as an intramuscular injection on a 2-dose vaccination schedule, 28 days apart (Day 1 and Day 29). Participants will be stratified by baseline flavivirus serostatus (seropositive and seronegative).

The study will comprise a Screening Phase (up to 28 days), a Vaccination Phase (up to 57 days), and a Long-Term Follow-up Phase (up to 12 months after last vaccination). Participants will have approximately 8 clinic visits with an additional 13 safety telephone calls. Study duration will be approximately 13 months for each participant. Participants will provide written informed consent before any study-specific procedures are performed.

Study vaccine dosing will begin with Cohort 1 (10 µg mRNA-1893 or placebo), followed sequentially by Cohort 2 (30 µg mRNA-1893 or placebo), Cohort 3 (100 µg mRNA-1893 or placebo), and Cohort 4 (250 µg mRNA-1893 or placebo).

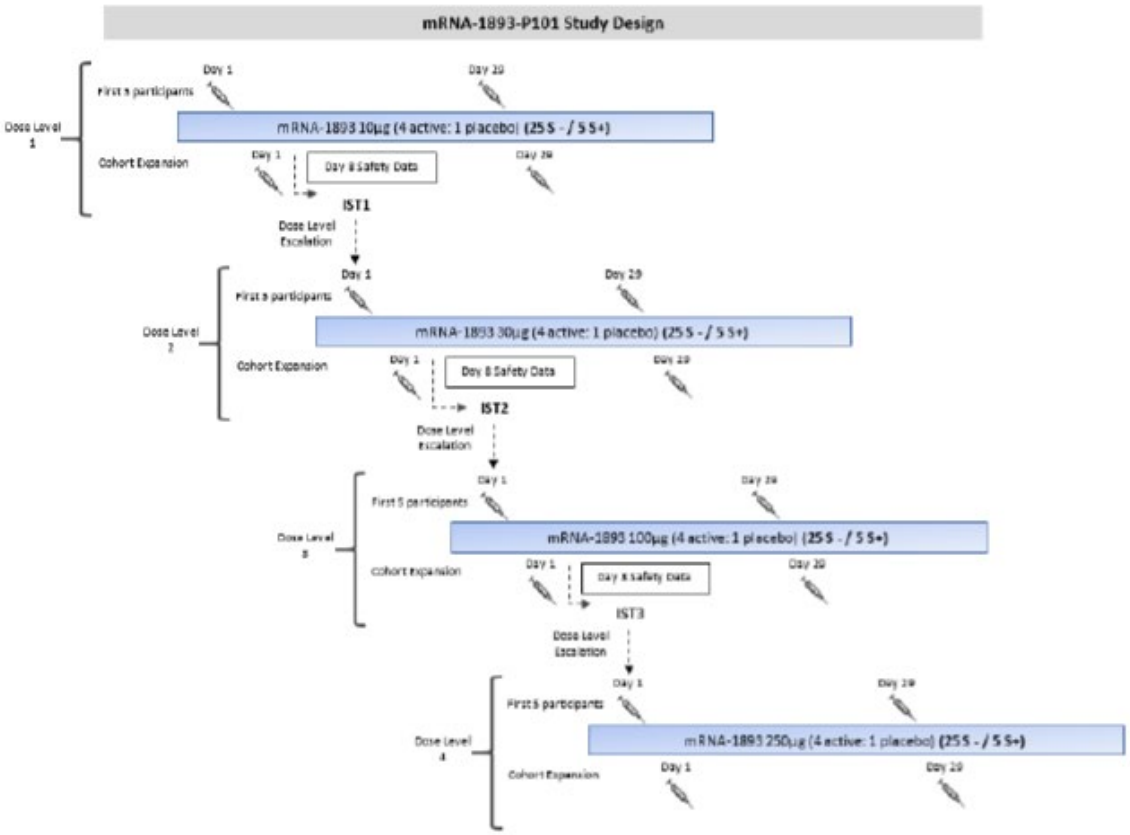
For each dose cohort (Cohort 1 through 4), Safety Oversight will be performed 7 days after the first 5 participants (all seronegative) are randomly assigned and receive the first study vaccination (Day 1). Once safety is confirmed, the remaining 25 participants in the dose level cohort will be randomly assigned to dosing. Seven days after all 30 participants in the cohort have received the first study vaccination, a blinded internal safety team (IST) that is not directly involved in the day-to-day activities of the study, will review all available safety data for the currently dosed cohort and any cumulative safety data of all cohorts as the trial advances to determine the acceptability to escalate to the next mRNA-1893 dose level. The 30 participants in the first cohort will continue to receive their second study vaccine dose on Day 29 (+7 days).

The blinded IST will oversee the safety of the trial and will review safety data to ensure adherence to the protocol, will monitor safety laboratory test results and reactogenicity, and may request input from the safety monitoring committee should the study meet pause rules or for any other study events that could potentially affect participant safety. The IST will approve escalation to the next higher dosing cohort after review of blinded safety data of the currently dosed cohort through 7 days after the first vaccination and any cumulative safety data of all cohorts as the trial advances.

A diagram of the dosing schema by cohort is shown in Figure 1.

Figure 1: Dosing Schema by Cohort

Figure 1: Dosing Schema by Cohort



Abbreviations: IST = internal safety team; S- = flavivirus seronegative; S+ = flavivirus seropositive.

Note: For each dose cohort (Cohorts 1 through 4), Safety Oversight will be performed 7 days after the first 5 participants (all flavivirus-seronegative) are randomly assigned and receive their first study vaccination (Day 1) before randomly assigning the remaining 25 participants in the cohort. Seven days after all 30 participants in the cohort have received the first study vaccination and review of all available safety data has been performed (ie, no safety concerns and pause rules have not been met), the IST will determine the acceptability to escalate to the next mRNA-1893 dose level.

5.2 Sample Size and Power

A total of 120 participants (30 participant per cohort) are planned for enrollment in the study and random assignment to study dosing. The sample size is considered sufficient to meet the study objective of identifying a dose and establishing initial safety results in a population of healthy adults in both endemic and nonendemic Zika regions. With 24 participants receiving mRNA-1893 in each dose level, there is a 92% probability to

observe at least 1 participant with an AE if the true incidence of the AE is 10% and a 70.8% probability if the true incidence of the AE is 5%.

5.3 Randomization

Participants will be randomly assigned (Day 1) in a blinded manner using the centralized Interactive Response Technology (IRT), with approximately 30 participants assigned to each cohort. Study vaccine dosing will begin with Cohort 1 (10 µg mRNA-1893 or placebo), followed sequentially by Cohort 2 (30 µg mRNA-1893 or placebo), Cohort 3 (100 µg mRNA-1893 or placebo), and Cohort 4 (250 µg mRNA-1893 or placebo). Within each cohort, participants will be randomly assigned in a blinded manner to receive either mRNA-1893 vaccine or placebo (4:1 mRNA-1893 vaccine to placebo) using the centralized IRT. Participants will be stratified according to flavivirus baseline serostatus.

In each cohort, the initial 5 participants (all seronegative) will be randomly assigned to vaccine or placebo (4:1 mRNA-1893 vaccine to placebo) before the remaining participants (n=25, 20 seronegative and 5 seropositive) are enrolled in the cohort.

Randomization by the centralized IRT will be in accordance with pre-generated randomization schedules, with only the unblinded pharmacy personnel having controlled access.

Dose group assignment in each cohort and stratification within each cohort is summarized in Table 1.

Table 1: Dose Group Assignment

Cohort	Dose Group Assignment	n	Flavivirus Status Stratification[a]		Total (Ratio)
			Status	n	
1	mRNA-1893 10 µg	24	+	4	30 (4:1)
			-	20	
	Placebo	6	+	1	
			-	5	
2	mRNA-1893 30 µg	24	+	4	30 (4:1)
			-	20	
	Placebo	6	+	1	
			-	5	
3	mRNA-1893 100 µg	24	+	4	30 (4:1)
			-	20	
	Placebo	6	+	1	
			-	5	
4	mRNA-1893 250 µg	24	+	4	30 (4:1)
			-	20	
	Placebo	6	+	1	
			-	5	
				Total	**120**

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

[a] In each cohort, the initial 5 participants enrolled will be flavivirus seronegative and randomly assigned to vaccine or placebo (4:1 mRNA-1893 to placebo) before the remaining participants (n=25, 20 seronegative and 5 seropositive) are enrolled in the cohort.

5.4 Blinding and Unblinding

This is an observer-blind study. The investigator, study participants, site monitors, and study staff will be blinded to the study vaccine administered until trial end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1893 (or placebo) to all participants. The designee(s) will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not

reveal the study vaccine identity to either the participant or the study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.

- An unblinded study monitor, not involved in other aspects of monitoring, will be assigned as the vaccine accountability monitor. They will have responsibilities to ensure that the site is following all proper vaccine accountability, preparation, and administration procedures.
- An unblinded statistician will provide a descriptive analysis of safety and immunological endpoints after the completion of each dosing cohort (refer to Section 7.8 for interim analyses), and perform evaluation of the pause rules criteria summarized in Table 3, Section 3.4.2.2 of the protocol.

6 Analysis Sets

The following analysis sets are defined: All Enrolled Participants Set, Intent-to-Treat (ITT) Set, Safety Set, and Per-Protocol (PP) Sets.

6.1 Analysis Sets for Safety

For the safety analysis sets described here, participants will be analyzed according to the vaccine received, rather than the vaccine to which the participant may have been randomly assigned.

The analyses of solicited safety data will be based on the Solicited Safety Sets; all other Safety analyses will be based on the Safety Set unless specified otherwise.

6.1.1 All Enrolled Participants Set

The All Enrolled Participants Set includes all participants who signed the ICF and were not screen failures. The All Enrolled Participants Set will only be used for descriptive purposes.

6.1.2 Safety Set

The Safety Set consists of all participants who received at least 1 dose of study vaccine (mRNA-1893 or placebo).

6.1.3 Solicited Safety Set (Solicited Local and Systemic Adverse Reactions)

A Solicited Safety Set is defined for each vaccination. The First (Second) Vaccination Solicited Safety Set consists of all participants in the Safety Set who have received the first

(second) study vaccination and have contributed any solicited AR data (local or systemic reactogenicity events) from the time of first (second) study vaccination through the following 7 days (Day 1 through Day 8 for first vaccination and Day 29 through Day 36 for second vaccination).

The Solicited Safety Sets will be used for the analyses of solicited AEs.

6.2 Analysis Sets for Immunogenicity

For the immunogenicity analysis sets described here, participants will be analyzed according to the treatment group they are randomized to, rather than the vaccine the participant received.

6.2.1 Intent-to-Treat Immunogenicity Set

The ITT set consists of all participants who were randomized to the study, regardless of protocol violations, unacceptable visit windows, missed vaccination, or missing data.

The ITT set will be used for supportive analyses at the final analysis only. If the ITT set differs from the overall PP set by more than 10% (ie, the difference between the number of participants in the ITT set and the number of participants in the overall PP set divided by the number of participants in the PP set is greater than 10%), then the primary immunogenicity analyses will also be conducted at the final analysis using the ITT set.

6.2.2 Per-Protocol Sets

The PP sets for analysis of immunogenicity data will be defined for each visit (ie, Visit 1 - Day 1, Visit 5 – Day 29, Visit 9 – Day 57 [Month 2], Visit 14 – Month 7, Visit 20 - Month 13 [EOS] PP sets) and consist of all participants who meet the following criteria:

- Did not have a major protocol deviation
- Received vaccine within the acceptable vaccination window and received full dose[s] of assigned vaccine
- Had immunogenicity samples taken within acceptable visit windows
- Had a pre-vaccination and the corresponding 1 post-vaccination serum sample available for testing. For the Visit 1 – Day 1 PP set, participants will only be required to have a pre-vaccination serum sample available for testing

Participants who miss the second vaccination may still be included in the PP set for Visit 5 immunogenicity data analysis. If the second vaccination occurs outside of the window, the subsequent data may need to be excluded from the PP set for visits occurring after the second vaccination.

In addition, an overall PP set will be defined for modeling across visits. A participant who is included in any one of the per-visit PP sets will be included in the overall PP set.

The PP sets will be used for the primary immunogenicity analyses at each interim analysis and at the final analysis.

7 Statistical Analysis

7.1 General Considerations

Participants will be identified in the listings by the participant identification number concatenated with the site number. For rescreened participants, only the data collected from the last screening will be presented in the data listings and included in the summaries.

Data from participants excluded from an analysis set will be presented in the data listings but not included in the calculation of summary statistics for the corresponding analysis set.

Although date of physical exam is collected in the eCRF, this data will not be presented in the data listings.

The following treatment groups will be used for summary purposes:

- Placebo
- mRNA-1893 10 µg
- mRNA-1893 30 µg
- mRNA-1893 100 µg
- mRNA-1893 250 µg
- mRNA-1893 Total

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation [SD], minimum, and maximum). See Appendix B for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of participants in that treatment within the analysis set of interest, unless otherwise specified.

For the change from Baseline safety summaries, Baseline will be defined as the last non-missing measurement (including repeated and unscheduled assessments) before the first vaccination.

For the immunogenicity analyses, Baseline will be defined as the last non-missing assessment collected at Visit Day 1.

Study Day relative to the first vaccination will be calculated as below:

- Study Day prior to the first vaccination will be calculated as: date of assessment/event – date of the first vaccination;
- Study Day on or after the date of the first vaccination will be calculated as: date of assessment/event – date of the first vaccination + 1;

Study Day relative to the most recent vaccination will be calculated as below:

- Study Day prior to the first vaccination will be calculated as: date of assessment/event – date of the first vaccination;
- Study Day on or after the date of the first vaccination but before the second vaccination (if applicable) will be calculated as: date of assessment/event – date of the first vaccination + 1;
- Study Day after the date of the second vaccination will be calculated as: date of assessment/event – date of the second vaccination + 1; if Study Day is on the same day as the second vaccination, date and time will be compared with the second vaccination date and time. If it is prior to the second vaccination, then study Day is calculated as: date of assessment/event – date of the first vaccination + 1; If it is after the second vaccination then Study Day is calculated as: date of assessment/event – date of the second vaccination + 1.

For GMT calculation, antibody values reported as below 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. Missing results will not be imputed.

The following timeframes will be defined for reporting safety data in this study:

- Vaccination: First vaccination on Day 1 to 28 days after last vaccination. If a participant receives two vaccinations, this stage starts at the first vaccination on Day 1 and continues through the 28th Day after the 2nd vaccination.
- Within 28 days of vaccination: Consists of all periods that begin with a vaccination and continue through the 28th Day after the vaccination. This is a subset of the vaccination stage. If a participant receives two vaccinations, this stage includes the two 28-Day periods that begin after each vaccination.
- Overall: Begins at the first vaccination on Day 1 and continues through the final safety call.

Analysis sets for the various analyses are defined in Section 6.

The 95% confidence interval (CI) for percentage will be obtained from SAS procedure of Proc Freq using Clopper-Pearson method. The 95% CI for GMT will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

Expected visit windows for all study assessments are detailed in Appendix A.

All analyses will be conducted using SAS Version 9.4 or higher.

7.2 Background Characteristics

7.2.1 Participant Disposition

The number of participants in the following categories will be summarized by treatment group (see Section 7.1) based on the ITT set:

- Safety Set
- Solicited Safety Sets
- PP Sets

The number and percentage of participants in each of the following disposition categories will be summarized by treatment group and serostatus, based on the ITT Set:

- Received each study vaccine
- Completed study (A participant who completed 12 months of follow up after the last vaccination received and completed the Month 13 procedures is considered to have completed the study.)

- Prematurely discontinued the study and the reason for discontinuation
- Prematurely discontinued vaccination and the reason for discontinuation

The number of participants that screen fail will be summarized along with the reason for screen failure.

Participant disposition, screen failure, randomization, and analysis set listings will be provided.

7.2.2 Demographics

Demographic information will be listed (including flavivirus serostatus at Screening) and summarized. Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Frequency counts will be tabulated for the categorical variables sex, race, and ethnicity. The summaries will be presented by flavivirus serostatus at Screening and by treatment group as defined in Section 7.1 for participants in the Safety set.

For screen failure participants, age (years), weight (kg), height (cm), BMI (kg/m^2), as well as sex, race, ethnicity will be presented in a listing.

In addition, an inclusion and exclusion criteria violation data listing will be provided.

7.2.3 Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history data will be presented in a listing.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization drug dictionary.

Use of analgesics and/or antipyretics will be recorded by participants on a diary card as absent or present, and participants will indicate if use was for treatment or prophylaxis.

The number and percentage of subjects for each common dictionary medical coded term during the 7-day follow-up period (ie, on the day of vaccination and the 6 subsequent days) and during the 28 day follow up period (ie, on the day of vaccination and the 27 subsequent days) will be summarized by treatment groups as defined in Section 7.1 after each vaccination for subjects in the Safety set. In addition, the number and percentage of

subjects using any analgesic or antipyretic or any prophylactic analgesic or antipyretic will be summarized.

Prior and concomitant medications will be presented in a listing.

7.4 Major Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the Internal Review Board (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. Protocol deviations will be assessed to determine if the deviation is a major or minor deviation and this assessment will be recorded in the protocol deviation review plan.

Major protocol deviations will be presented in a listing.

7.5 Study Vaccine Administration

Study vaccine administration data will be presented in a listing.

7.6 Safety Analysis

Safety assessments will include monitoring and recording of solicited AEs (local and systemic reactogenicity events) and unsolicited AEs, SAEs, AESIs, AEs leading to study withdrawal, MAAEs; clinical laboratory test results (hematology, serum chemistry, and coagulation); vital sign measurements; and physical examination findings. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials [DHHS 2007] will be used to categorize unsolicited AEs, abnormal clinical laboratory test results, and vital sign measurements.

All safety analyses will be based on the Safety set, except that the analyses of solicited AEs will be based on the Solicited Safety sets.

7.6.1 Solicited Adverse Reactions

The term “reactogenicity” refers to selected signs and symptoms (ARs) occurring after vaccine administration that the participants are systematically asked to record. Participants will record such occurrences in a diary card on the day of each vaccine administration and for the 6 days after vaccine administration.

The local solicited ARs include injection site pain, injection site erythema, and injection site induration/swelling.

The systemic solicited ARs include fever, generalized myalgia (muscle ache or pain), generalized arthralgia (joint ache or pain), headache, fatigue/malaise (unusual tiredness), nausea/vomiting, chills, and rash.

For erythema, swelling, and fever, grade will be derived based on the measurement recorded on the diary card as noted in Table 2. Other events will be assessed for grade by the investigator based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials [DHHS 2007] and recorded in the eCRF.

Table 2: Toxicity Grads for Erythema, Swelling, and Fever

	Grade 1	Grade 2	Grade 3	Grade 4
Erythema	21 – 50 mm	51 – 100 mm	> 100 mm	--
Swelling	21 – 50 mm	51 – 100 mm	> 100 mm	--
Fever	38.0 – 38.4°C	38.5 – 38.9°C	39.0 – 40.0°C	> 40.0°C

Any solicited AR that meets any of the following criteria will be entered as an AE in the eCRF:

- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator
- Solicited local or systemic AR lasting beyond 7 days post vaccination
- Solicited local or systemic AR that leads to participant withdrawal from vaccine
- Solicited local or systemic AR that otherwise meets the definition of an SAE
- Laboratory test result or vital sign measurements with a toxicity score of Grade 3 or greater or that is deemed clinically significant by the investigator for any grade

The percentage of participants who report each individual solicited local AR and solicited systemic AR from the time of study vaccination through the following 6 days (Day 1 through Day 7 and Day 29 though Day 35) will be tabulated by grade (including grades 1, 2, 3, and any grade >0), treatment group as defined in Section 7.1, and vaccination (first or second). These summaries will also be presented separately for flavivirus seropositive and seronegative participants.

Duration (in days) of each solicited AR will be summarized by treatment group and vaccination.

All solicited ARs, local solicited ARs, systemic solicited ARs, solicited ARs that are still on-going 6 days after vaccination, and solicited rash events will be presented in separate data listings.

7.6.2 Adverse Events

An unsolicited AE is any AE reported by the participant that is either (1) not specified as a solicited AE in the protocol or (2) specified as a solicited AR in the protocol, but its onset occurs outside of the protocol-defined post vaccination period for reporting solicited AEs (ie, for the 7 days after each vaccination). A solicited ARs that meet the criteria for an SAE will also be recorded as an unsolicited AE.

A treatment-emergent AE (TEAE) is defined as any AE not present before exposure to vaccine or any AE already present that worsens in intensity or frequency after exposure. Only TEAEs are collected in this study.

An MAAE is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by treatment, vaccination (first or second) and overall. Summaries for each vaccination will include AEs that occur during the 28 -day follow-up period after each vaccine.

All summaries of unsolicited AEs will present number and percentage of subjects in each category. For those summaries presented by PT, the preferred terms will be sorted in descending order of frequency within the mRNA-1893 treatment group.

7.6.2.1 Overview of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of participants who experience the following will be presented:

- All unsolicited TEAEs
- All unsolicited serious TEAEs
- All unsolicited TEAEs leading to death

- All unsolicited TEAEs leading to vaccination discontinuation
- All unsolicited TEAEs of grade 3 or 4
- All unsolicited TEAEs of special interest
- All unsolicited medically-attended TEAEs

The table will also include number and percentage of participants with unsolicited, treatment-related TEAEs in each of the above categories.

The overall summary will also be summarized separately for flavivirus seropositive and seronegative participants.

In addition, listings containing individual participant data for TEAEs, TEAEs leading to vaccination discontinuation, SAEs, AESIs, and medically-attended TEAEs will be provided separately.

7.6.2.2 TEAEs by Preferred Term

The following summary tables of TEAEs will be provided by MedDRA PT using frequency counts and percentages (i.e., number and percentage of participants with an event). When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented and an AE with missing severity will be counted as Grade 3/severe in the severity summaries. Only the strongest relationship level will be presented and an AE with missing relationship will be counted as related in the relationship summaries.

- All unsolicited TEAEs
- All unsolicited TEAEs by relationship to the study vaccine
- All unsolicited TEAEs by toxicity grade
- All unsolicited TEAEs occurring within 28 days of any vaccination by vaccination
- All unsolicited TEAEs within 28 days of any vaccination by vaccination and toxicity grade

7.6.2.3 TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of participants with an event) for all participants, for all flavivirus seropositive participants and for all flavivirus seronegative participants. When summarizing the number and percentage of participants with an event, participants with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented and an AE with missing severity will be counted as Grade 3/severe in the severity summaries. Only the strongest relationship level will be presented and an AE with missing relationship will be counted as related in the relationship summaries.

- All unsolicited TEAEs
- All unsolicited treatment-related TEAEs
- All unsolicited TEAEs through 7 days after any vaccination
- All unsolicited treatment-related TEAEs through 7 days after any vaccination
- All unsolicited TEAEs of Grade 3 or higher through 7 days after any vaccination
- All unsolicited treatment-related TEAEs of Grade 3 or higher through 7 days after any vaccination
- All unsolicited TEAEs of Grade 2 or higher through 7 days after any vaccination
- All unsolicited treatment-related TEAEs of Grade 2 or higher through 7 days after any vaccination
- All unsolicited TEAEs of Grade 3 or higher through 28 days after any vaccination
- All unsolicited treatment-related TEAEs of Grade 3 or higher through 28 days after any vaccination
- All unsolicited TEAEs of Grade 2 or higher through 28 days after any vaccination
- All unsolicited treatment-related TEAEs of Grade 2 or higher through 28 days after any vaccination

- All unsolicited TEAEs within 60 minutes after any vaccination
- All unsolicited treatment-related TEAEs within 60 minutes after any vaccination
- All unsolicited serious TEAEs after any vaccination
- All unsolicited serious treatment-related TEAEs after any vaccination
- All unsolicited TEAEs of special interest after any vaccination
- All unsolicited treatment-related TEAEs of special interest after any vaccination

7.6.3 Clinical Laboratory Evaluations

All laboratory test results will be presented in the data listings. The results that are outside the reference ranges will be flagged in the data listings. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any safety laboratory will be listed separately. If a participant has a laboratory test with Grade 2 or higher abnormality at any post vaccination visit, then all results for that participant and laboratory test will be presented in the listing.

For continuous hematology, serum chemistry, and coagulation measurements, the observed values and changes from Baseline will be summarized at each scheduled visit by treatment groups as defined in Section 7.1. Shift from baseline in the toxicity grades to the worst post-vaccination result will be summarized by treatment group and vaccination (first or second). All scheduled and unscheduled assessments will be considered when determining the worst post-vaccination result.

Incidence of laboratory abnormalities of Grade 2 or higher after any vaccination and through 7 days after any vaccination will be summarized by treatment group.

7.6.4 Vital Signs

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values meeting the toxicity grading criteria will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a participant has a vital sign result with Grade 2 or higher

abnormality at any post vaccination visit, then all results for that participant and vital sign measurement will be presented in the listing.

Observed values and changes from Baseline for all vital sign measurements will be summarized at each scheduled visit by treatment groups as defined in Section 7.1. Shift from baseline in the toxicity grades to the worst post-vaccination result will be summarized by treatment group and vaccination (first or second).

Incidence of vital sign abnormalities of Grade 2 or higher after any vaccination and through 7 days after any vaccination will be summarized by treatment group.

7.7 Immunogenicity Analysis

The GMT will be calculated by averaging the log-transformed titers and then transforming back to the original scale as in the following formulas:

$$10^{\left\{\frac{\sum_{i=1}^{n} log_{10}(t_i)}{n}\right\}} \text{ or } e^{\left\{\frac{\sum_{i=1}^{n} log_e(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers. The 95% Cis are also calculated on the log-transformed values and the transforming back to the original scale.

7.7.1 Immunogenicity Assessments

The following immunogenicity assessments will be performed: nAb against ZIKV by PRNT, nAb against ZIKV by additional neutralization assays (including microneutralization [MN] and reporter virus neutralization test [RVNT]), bAb against ZIKV by ELISA binding assay, and IgG and IgM antibodies against envelope- and NS1-based antigens by ELISA or equivalent methodology to flaviviruses.

All immunogenicity data will be presented in a data listing.

7.7.2 Analysis of nAb against ZIKV by PRNT

The nAb against ZIKV by PRNT will be summarized by treatment group and scheduled visit as follows:

- GMT of nAb against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT with corresponding 95% CIs.

- GMT of nAb against ZIKV in initially flavivirus seronegative participants at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT with corresponding 95% CIs.
- GMT of nAb against ZIKV in initially flavivirus seropositive participants at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT with corresponding 95% CIs.
- Percentage of participants who seroconverted from Day 1 (baseline) to Day 29, from Day 1 to Day 57, from Day 1 to Month 7, and from Day 1 to Month 13.
- Proportion of initially seronegative participants with a seroresponse at Day 29, Day 57, Month 7, and Month 13 as measured by PRNT.
- Proportion of initially seropositive participants with a 2-fold or 4-fold increase in nAb titers as compared with baseline at Day 29, Day 57, Month 7, and Month 13 as measured by PRNT.
- Reverse cumulative distribution of nAb against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by PRNT.

7.7.3 Analysis of nAb against ZIKV by Microneutralization Assay and Reporter Virus Neutralization Test

The nAb against ZIKV as measured by MN and RVNT will be summarized by treatment group and scheduled visit as follows:

- GMT of nAb against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by MN and RVNT with corresponding 95% CIs.
- GMT of nAb against ZIKV in initially flavivirus seronegative participants at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by MN and RVNT with corresponding 95% CIs.
- GMT of nAb against ZIKV in initially flavivirus seropositive participants at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by MN and RVNT with corresponding 95% CIs.
- Percentage of participants who seroconverted from Day 1 (baseline) to Day 29, from Day 1 to Day 57, from Day 1 to Month 7, and from Day 1 to Month 13.
- Proportion of initially seronegative participants with a seroresponse at Day 29, Day 57, Month 7, and Month 13 as measured by MN and RVNT.

- Proportion of initially seropositive participants with a 2-fold or 4-fold increase in nAb titers as compared with baseline at Day 29, Day 57, Month 7, and Month 13 as measured by MN and RVNT.

7.7.4 Analysis of bAb against ZIKV by ELISA Binding Assay

The bAb against ZIKV by ELISA binding assay will be summarized by treatment group and scheduled visit as follows:

- GMC of bAb against ZIKV at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay with corresponding 95% CIs.
- GMC of bAb against ZIKV in initially flavivirus seronegative participants at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay with corresponding 95% CIs.
- GMC of bAb against ZIKV in initially flavivirus seropositive participants at Day 1, Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay with corresponding 95% CIs.
- Percentage of participants who seroconverted from Day 1 (baseline) to Day 29, from Day 1 to Day 57, from Day 1 to Month 7, and from Day 1 to Month 13.
- Proportion of initially seronegative participants with a seroresponse at Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay.
- Proportion of initially seropositive participants with a 2-fold or 4-fold increase in bAb concentration as compared with baseline at Day 29, Day 57, Month 7, and Month 13 as measured by ELISA binding assay.

7.7.5 Analysis of IgG and IgM antibodies against envelope- and NS1- based antigens

The GMC for IgG and IgM antibodies against envelope- and NS1-based antigens present in serum collected at baseline and at end of study measured as antibody binding by ELISA or equivalent methodology to flaviviruses will be summarized by treatment group with corresponding 95% CIs.

7.8 Interim Analyses

Once all participants from a cohort have completed the Vaccination Phase through Visit 9, the database will be locked for that cohort and safety and immune test results will be analyzed through 28 days following the second vaccination by an unblinded statistician. As dose escalation occurs, cumulative analyses will be included for each subsequent data lock

to allow for all prior dosing cohorts to be analyzed by dose assignment, and in aggregate for mRNA-1893 exposure. Immunogenicity and safety data will be summarized for each treatment group, including summarization of change from baseline in each group where applicable.

8 Changes and Clarifications from Planned Analyses in Protocol

The following changes were made to the planned analyses:

- In protocol section 3.6.5, the All Enrolled Participants Set was defined as including all participants who signed the ICF. The definition has been changed to: The All Enrolled Participants Set will include all participants who signed the ICF and did not screen fail.
- In protocol section 3.6.6.2, it indicates that "the difference in the proportion of participants with AEs will be provided, comparing each dose level with placebo pooled across all cohorts." The actual difference will not be computed. The proportions for each dose level and pooled placebo will be presented and is considered sufficient for comparison.

9 References

Department of Health and Human Services (DHHS), National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events. Version 2.0. November 2014. [cited 2019 April 13]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daids-ae-grading-table-v2-nov2014-highlightedchanges.pdf.

10 List of Appendices

10.1 Appendix A Analysis Visit Windows for Safety and Immunogenicity Analysis

Table 3 Visit Window Mapping Rules

Labs (Hematology, Chemistry, and Coagulation) and Vital Signs		
Visit	**Target Study Day**	**Visit Window**
Day 1	Date of First Vaccination (1)	Pre-dose
Day 1, 1 hour postdose – Vitals only	1	≥ 1 hour post-dose
Day 8 - Labs only	8	[8,11]
Day 29	Date of Second Vaccination (29)	[29,36]
Day 29, 1 hour postdose – Vitals only	29	≥ 1 hour post-dose
Day 36 - Labs only	36	[36,39]
Day 57 (Month 2) – Labs only	57	[50,64]
Adverse Events		
Stage	**Vaccination**	**Target Time Frame**
Vaccination	All	[1, 57]
Short-Term Follow-up	First	[1,29]
	Second	[29,57]
Long-Term Follow-up	First	NA
	Second	[57, Month 12 Safety Call]
Overall	All	[1, Month 12 Safety Call]

Immunogenicity		
Visit	**Target Study Day**	**Visit Window**
Day 1	Date of First Vaccination (1)	Pre-dose
Day 29	29	[29,36]
Day 57 (Month 2)	57	[50,64]
Month 7	196	[182,210]
Month 13	364	[343, 385]

10.2 Appendix B Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables

The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

10.3 Appendix C Imputation Rules for Missing or Partial Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first Day of the month.
    b. If DAY and Month are both missing, use the first Day of the year.
    c. If DAY, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first vaccination for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last Day of the month.
    b. If DAY and Month are both missing, use the last Day of the year.
    c. If DAY, Month and year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 4 Prior, Concomitant, and Post Categorization of a Medication

	Stop Date		
Start Date	**< Date of First Vaccination**	**≥ Date of First Vaccination and ≤ 28 days after Last Vaccination**	**> 28 days after Last Vaccination [2]**
< Date of First Vaccination [1]	P	PC	PCA
≥ Date of First Vaccination and ≤ 28 days after Last Vaccination	-	C	CA
> 28 days after Last Vaccination	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date

10.4 Appendix D: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start/stop dates are defined below:

1. Missing or partial AE start date:
    a. If only DAY is missing, use the first Day of the month, unless:
        i. The AE end date is after the date of first vaccination or is missing AND the start Month and year of the AE coincide with the start Month and year of the first vaccination. In this case, use the date of first vaccination

b. If DAY and Month are both missing, use the first Day of the year, unless:

i. The AE end date is after the date of first vaccination or is missing AND the start year of the AE coincides with the start year of the first vaccination. In this case, use the date of first vaccination

c. If DAY, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first vaccination, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partial AE end dates will not be imputed

10.5 Appendix E: Schedule of Events

Please refer to Table 5 in Section 6.1 Appendix 1: Schedule of Events in the protocol.

10.6 Appendix F: Immunogenicity Assessments

The following laboratory assays are planned to measure the immune response to mRNA-1893 (Table 5):

- nAb against ZIKV will be measured using PRNT, MN, RVNT and possibly additional neutralization assays.
- bAb against ZIKV will be measured by ELISA.
- IgG and IgM antibodies against envelope- and NS1-based antigens will be measured by ELISA or equivalent methodology to flaviviruses

- **Table 5: Immunogenicity Against Zika Virus**

Material	Component	Method	Unit
Serum	Neutralizing antibodies against ZIKV	PRNT	Fold dilution (titer)
Serum	Neutralizing antibodies against ZIKV	Reporter Virus Neutralization Test	Fold dilution (titer)
Serum	Neutralizing antibodies against ZIKV	Microneutralization Assay	Fold dilution (titer)
Serum	binding antibodies against ZIKV	ELISA	Fold rise (concentration)
Serum	IgG and IgM antibodies against envelope- and NS1-based antigens	ELISA	Fold rise (concentration)

Abbreviations: ELISA, enzyme-linked immunosorbent assay; PRNT, Plaque Reduction Neutralization Test.

PPD	PPD Biostatistics and Programming
	Statistical Analysis Plan (SAP) Client Approval Form

Client:	ModernaTX, Inc.
Protocol Number:	mRNA-1893-P101

Document Description:	Final Statistical Analysis Plan
SAP Title:	A PHASE 1, RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF ZIKA VACCINE mRNA-1893 IN HEALTHY FLAVIVIRUS SEROPOSITIVE AND SERONEGATIVE ADULTS
SAP Version Number:	3.0
Effective Date:	25MAY2021

Author(s):

For PPD: PPD

Approved by:

PPD

PPD ModernaTX, Inc. Date *(DD-MMM-YYYY)*

PPD

PPD ModernaTX, Inc. Date *(DD-MMM-YYYY)*