Moderna Therapeutics, Inc.

VAL-181388-P101

A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF VAL-181388 IN HEALTHY ADULTS IN A NON-ENDEMIC CHIKUNGUNYA REGION

19 September 2018

Statistical Analysis Plan

Version Final 2.0

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Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CHIKV	chikungunya virus
CI	confidence interval
CS	clinically significant
CSR	Clinical study report
eCRF	electronic case report form
EOS	end-of-study
GMR	geometric mean ratio
GMT	geometric mean titer
ICF	informed consent form
IgG	immunoglobulin G
IM	intramuscular
IST	internal safety team
ITT	Intent-to-Treat
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NCS	not clinically significant
PP	Per-Protocol
PT	preferred term
SAE	serious adverse event
SAS	Statistical Analysis System
SD	Standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TLFs	Tables, listings, and figures
ULOQ	upper limit of quantification
WHODrug	World Health Organization Drug

1. Administrative Structure

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

This statistical analysis plan has been written according to protocol VAL-181388-P101, Version 4.0, dated 30 August 2018.

2. Introduction

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus posing a significant public health problem in tropical and subtropical regions. While chikungunya has been present in Africa for centuries, it has recently caused outbreaks and epidemics in new regions reflecting the increasing distribution of the *Aedes* mosquito. A chikungunya epidemic beginning in 2004 in Kenya, which spread to the Indian Ocean islands and to India, and was exported to nearly all regions of the world via infected travelers, resulted in millions of infected individuals and brought chikungunya to the attention of the western world. As of April 2016, chikungunya cases had been reported in 103 countries and territories around the world, including 46 countries and territories throughout the Americas (Centers for Disease Control and Prevention 2016). There are an estimated 3 million cases of chikungunya globally.

There are currently no effective therapies or approved vaccines to treat or prevent chikungunya, and effective mosquito control has proven challenging, even in higher income countries. Mosquito nets have limited effectiveness against the daytime-biting *Aedes* mosquito. Therefore, there is a need for a safe and effective prophylactic vaccine.

Of the new approaches currently in development, virus-like particle vaccines and live-attenuated vaccines show the greatest potential from preclinical data (Wang et al 2008; Akahata et al 2010; Darwin et al 2011; Brandler et al 2013). However, there are significant potential drawbacks with these 2 vaccine approaches. The virus-like particle-based vaccines are typically challenging to manufacture, particularly within the context of a disease of greatest relevance to developing countries where it is desirable to keep the technology simple and cost of goods low. The live-attenuated vaccines, on the other hand, carry the well-known safety concerns normally associated with this type of technology (potential of break-through infections and possible central nervous system sequelae,

depending on the chosen virus backbone). Based on encouraging preclinical data with VAL-181388 and other similar messenger RNA (mRNA)-based vaccine candidates in the development pipeline, the Sponsor believes that VAL-181388 has the potential to be a tolerable and effective prophylactic vaccine against CHIKV.

3. Objectives

3.1. Primary Objective

The primary objective of this study is to assess the safety of VAL-181388 relative to placebo.

3.2. Secondary Objectives

The secondary objective of this study is to determine the immunogenicity of 3 dose levels of VAL-181388 to inform the choice of dose for further development of this vaccine. Immunogenicity assessment will be based on changes from baseline in the following:

- Serum neutralizing antibody titers to CHIKV
- Serum binding antibody titers to CHIKV-specific proteins

3.3. Exploratory Objectives

The exploratory objectives of this study are to:

- Assess the cross-reactivity of serum antibodies to related viruses, including alphaviruses and flaviviruses
- Explore other assays to characterize the immune response to CHIKV

4. Investigational Plan

4.1. Overall Study Design and Plan

This is a Phase 1, first-in-human, randomized, observer-blinded, placebo-controlled, dose escalation study to evaluate the safety and immunogenicity of 3 dose levels of VAL-181388 in healthy adult subjects (18 to 49 years of age, inclusive). VAL-181388 is an mRNA-based vaccine being developed for prevention of disease associated with CHIKV infection.

This is a 2-part study, with Part A including dose escalation and safety and immune testing through 28 days following the final vaccination. Once subjects complete Part A they will transition to Part B. Part B is a continued safety follow-up through 12 months and an assessment of immunogenicity and immune persistence at approximately 6 and 12 months after final vaccination.

Part A

In Part A, sequential dose escalation of VAL-181388 is planned in 3 dose level cohorts (25, 50, and 100 μg) with each subject receiving 2 vaccinations separated by 28 days. Subjects will be randomly assigned to receive either VAL-181388 or placebo.

For each cohort, a sentinel safety group of 4 subjects will be enrolled who will be randomly assigned to VAL-181388 or placebo (3:1) and followed for 7 days after the first vaccination with review of reactogenicity and safety laboratory results prior to randomizing the remainder of the cohort.

Dose Level Cohort Assignments: VAL-181388 (or placebo) administered intramuscular (IM) at Visit 1 and a second dose administered 28 days later (Visit 4).

Cohort 1 (N = 20): 25 μg VAL-181388 or placebo (ratio = 3:1)

Cohort 2 (N = 20): 50 μg VAL-181388 or placebo (ratio = 3:1)

Cohort 3 (N = 20): 100 μg VAL-181388 or placebo (ratio = 3:1)

VAL-181388 (or placebo) will be administered as an IM injection (0.5 mL) into the deltoid muscle, preferably in the non-dominant arm, as a 2-dose schedule; the first dose will be given at Visit 1 followed by a second dose 28 days later. VAL-181388 accountability, dose preparation, and administration will be performed by unblinded pharmacy personnel or unblinded designees who will not participate in any other aspect of the study. The remainder of the site staff and all subjects will remain blinded to treatment assignment.

Subjects will be instructed on recording solicited (local and systemic reactogenicity events) and unsolicited adverse events (AEs), temperature, and medications (prescription or over-the-counter) on their memory aid (ie, diary card). Subjects will also be asked to call/return to the clinic within 24 hours if reactogenicity reaches Grade 3 or higher during the first 7 days following vaccination. As standard practice, a reminder call will be made to

the subject by the site at least once during the first 7 days following each vaccination to answer any questions and ensure that the memory aid is being completed correctly and consistently.

Safety assessments will include toxicity grading of solicited (local and systemic reactogenicity events) and unsolicited AEs, vital sign measurements, physical examination findings, and clinical laboratory test results for hematology, serum chemistry, coagulation, and urinalysis. All unsolicited AEs will be collected and additional specific categories will include serious AEs (SAEs); AEs of special interest (AESIs); and medically attended AEs. Subjects will self-report (using a memory aid) solicited (local and systemic reactogenicity events) and unsolicited AEs and medication usage (over-the-counter and prescription) through 28 days after each vaccination. In addition, subjects will be instructed to measure their oral temperature daily for the first 7 days post vaccination and record that measure on the memory aid. At applicable clinic visits, the investigator will review the entries on the memory aid with the subject to ensure consistency.

Part A is concluded for each subject when they return to the clinic for Visit 7 (28 days after final vaccination). At that time, subjects will transition to Part B of the study.

Part B

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

Once entered into Part B, each safety contact will occur by telemedicine (eg, telephone, text message, internet) every 28 (±7) days, and blood samples for immune persistence will be collected from each subject on Visit 12 (168 [±15] days after the second vaccination) and Visit 19 (364 [+15] days after the second vaccination) of the study. Each safety contact will capture outcomes of any AESI or SAE that remains unresolved since the last visit or is newly identified through scripted query.

The telemedicine visits may require additional data through medically attended visits, in addition to medications and vaccinations taken by the subject during this time. Subjects will have consented during study enrollment to allow access to additional medical records

needed to complete Part B, thereby allowing the blinding of the treatment assignment to be maintained.

4.2. Study Endpoints

The following are the safety (primary) endpoints:

Part A:

- Solicited AEs (local and systemic reactogenicity events) collected for 7 days following each vaccination with toxicity grading
- Unsolicited AEs collected for 28 days following each vaccination; additional classification if serious, medically attended, or an AESI
- Safety laboratory test results (serum chemistry, hematology, coagulation, and urinalysis) with toxicity grading
- Vital sign measurements with toxicity grading and physical examination findings

Part B:

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

The immunogenicity assessments are as follows:

Part A:

- Serum neutralizing antibody titers to CHIKV proteins (baseline and 28 days after each vaccination)
- Serum binding antibody titers (immunoglobulin G [IgG]) to CHIKV proteins (baseline and 28 days after each vaccination)
- Exploratory antibody assays may be performed with excess serum to assess for cross-reactivity to related viruses at the discretion of the Sponsor

- Additional exploratory assays based upon current research may be performed with excess serum to better characterize the immune response to the CHIKV proteins at the discretion of the Sponsor

Part B:

- Serum neutralizing antibody titers to CHIKV (at 6 and 12 months after the last vaccination)
- Serum binding antibody titers (IgG) to CHIKV-specific proteins (at 6 and 12 months after the last vaccination)
- Exploratory antibody assays may be performed with excess serum to assess for cross-reactivity to related viruses at the discretion of the Sponsor
- Additional exploratory assays based upon current research may be performed with excess serum to better characterize the immune response to the CHIKV proteins at the discretion of the Sponsor

5. General Statistical Considerations

All data collected will be presented in listings. Subjects will be identified in the listings by the subject identification number concatenated with the site number.

Data from subjects 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.

Data from subjects receiving placebo will be pooled across cohorts for all presentations.

Unless otherwise specified, the following treatment groups will be used for summary purposes:

- 25 μg VAL-181388
- 50 μg VAL-181388
- 100 μg VAL-181388
- Placebo

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

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, and confidence intervals (CIs) will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places.

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 subjects 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 assessment before the first vaccination.

Study day will be calculated relative to the most recent vaccination. Study day prior to the first vaccination will be calculated as: date of assessment/event – date of first vaccination; study day on or after the date of first vaccination but before the second vaccination (if applicable) will be calculated as: date of assessment/event – date of first vaccination + 1; study day on or after the date of second vaccination will be calculated as: date of assessment/event – date of second vaccination + 1.

Antibody values 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. Missing results will not be imputed.

All analyses will be conducted using Statistical Analysis System (SAS) Version 9.3 or higher.

5.1. Sample Size

Approximately 60 subjects (20 per cohort) are planned to be randomized, 15 receiving VAL-181388 and 5 receiving placebo within each cohort. Formal sample size calculations were not performed as this is a descriptive safety and immunogenicity study with no formal null hypotheses being tested.

5.2. Randomization and Blinding

Within each dose level cohort, 20 subjects will be randomly assigned to receive either VAL-181388 (25, 50, or 100 μg) or placebo in an overall ratio of 3:1. The first 4 subjects within each dose level cohort will be randomly assigned to receive VAL-181388 (25, 50, or 100 μg) or placebo in a 3:1 ratio. Only after review by the internal safety team (IST) of the blinded safety data (reactogenicity, safety laboratory results, and AEs) through 7 days following the first vaccination of the sentinel safety lead-in for each cohort planned, will approval be given to allow randomization of the remainder of that cohort. The remaining 16 subjects within each dose level cohort will be randomly assigned to receive either VAL-181388 (25, 50, or 100 μg) or placebo in a 3:1 ratio.

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

- Unblinded pharmacy personnel (of limited number) will be assigned to perform drug accountability procedures and to prepare and administer VAL-181388 (or placebo) to all subjects. The unblinded pharmacy personnel will have no other study functions other than study drug management, documentation, accountability, preparation, and administration. They will not be involved in subject evaluations and will not reveal the study drug identity to either the subject or study site personnel involved in the conduct of the study, except in the case of an emergency.

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

- An unblinded statistician will provide a descriptive analysis of safety and immunological endpoints after the completion of each dosing cohort. The interim analyses of immunogenicity data will be performed as outlined in Section 11.

The treatment assignment will be concealed by having the unblinded pharmacy personnel prepare the study drug in a secure location that is not accessible to other study personnel. The syringe used will maintain the blind at the time of vaccination (eg, a sleeve will be used should the vaccine substance be distinguishable in appearance between the VAL-181388 and placebo). The unblinded pharmacy personnel will conduct the vaccination procedure. Once the vaccination is completed, the blinded study staff will take over further assessments and interactions with the subjects. Access to the randomization code will be strictly controlled at the pharmacy.

5.2.1. Breaking the Blind

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

5.3. Analysis Sets

The following analysis sets will be used: All Enrolled Subjects set, Randomized set, Safety set, Per-Protocol (PP) sets and Intent-to-Treat (ITT) sets.

5.3.1. All Enrolled Subjects Set

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

5.3.2. Randomized Set

The Randomized set will include all subjects who were randomly assigned to the study including sentinel safety subjects. This set will only be used for descriptive purposes.

5.3.3. Safety Set

The Safety set will include all subjects who received at least 1 dose of study drug (VAL-181388 or placebo). All subjects in the Safety set will be analyzed according to the study drug actually received and not according to the study drug the subject was randomly assigned to receive, in the event there is a discrepancy.

5.3.4. Per-Protocol Sets

The PP sets will be defined separately for Part A and the entire study to support the primary assessments of immunogenicity in Part A and immune persistence in Part B.

The Primary PP set will include all subjects in the Randomized set who, in Part A (Visit 1 through Visit 7), did not observe any major protocol violation, received vaccination within the acceptable vaccination window (their full dose(s) of assigned study drug), had blood collection within accepted visit windows, and had both a pre-vaccination blood sample and at least 1 blood sample at Visit 4 or Visit 7 available for immunogenicity testing.

The Persistence PP set will include all subjects in the Primary PP set who, in Part B (Visit 8 through Visit 19), did not observe a major protocol violation, had blood collection within accepted visit windows, and had at least 1 blood sample at Visit 12 or Visit 19 available for immunogenicity testing.

All subjects in the PP sets will be analyzed according to the study drug the subject was randomly assigned to receive and not according to what was actually received, in the event there is a discrepancy. In the case where there is not a paired sample for the specific time point that data will not be included in the analysis. The process for determining major protocol violations will be provided as a separate study document.

5.3.5. Intent-to-Treat Sets

The ITT sets will provide supportive analyses, and will be defined separately for Part A and the entire study to support the primary assessments of immunogenicity in Part A and immune persistence in Part B.

The Primary ITT set will include all subjects in the Randomized set who, in Part A (Visit 1 through Visit 7), had at least 1 post-vaccination blood sample at Visit 4 or Visit 7 available for immunogenicity testing regardless of protocol violations, exceeded visit windows, missed vaccination, or missing data.

The Persistence ITT set will include all subjects in the Primary ITT set who, in Part B (Visit 8 through Visit 19), had at least 1 blood sample at Visit 12 or Visit 19 available for immunogenicity testing regardless of protocol violations, exceeded visit windows, missed vaccination, or missing data.

All subjects in the ITT sets will be analyzed according to the study drug the subject was randomized to receive and not according to what was actually received, in the event there is a discrepancy.

6. Subject Disposition

6.1. Disposition

Subjects' disposition will be presented in a data listing.

The total number of subjects who receive each vaccination, who complete and discontinue the study, and who are included in each analysis set will be summarized. The number of subjects, who discontinue from the study, both overall and according to the reasons for discontinuation, will also be summarized. The reason for discontinuation can be:

- AE
- death
- lost to follow-up
- non-compliance with study drug
- physician decision
- pregnancy
- protocol deviation
- site terminated by sponsor
- study terminated by sponsor
- withdrawal by subject

- other

The summaries will be presented by treatment group as defined in Section 5.

6.2. Inclusion and Exclusion Criteria Deviations

Inclusion and exclusion criteria deviations will be presented in a listing.

6.3. Major Protocol Violations

Major protocol violations will be presented in a listing. These data will be provided as a .csv file from agreements made at the Protocol Deviation Meeting at a minimum prior to database lock. SAS listings will be provided to support this meeting, which is held after the completion of each dose level (or every six months) and just prior to database lock.

7. Demographics and Baseline Characteristics

7.1. Demographics

Demographic information will be listed and summarized. Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years, calculated as the integer part of [date of informed consent - date of birth]/365.25), weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Frequency counts will be tabulated for the categorical variables gender, race, and ethnicity. The summaries will be presented by treatment group as defined in Section 5 for subjects in the Safety set.

7.2. Medical History

Medical history data will be presented in a listing.

8. Treatments and Medications

8.1. Prior and Concomitant Medications

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

In Part A of the study, concomitant medications include all medications (including vaccination outside of trial) taken by the subject from the time of signing the informed consent form (ICF) through 28 days after the second vaccination (Visit 7) and will be

recorded in the eCRF. In Part B, receipt of immunomodulators (including vaccines), immunosuppressants, or other concomitant medications that could potentially impact immune response will be collected through the end-of-study (EOS) visit.

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

Prior and concomitant medication will be coded using the WHO Drug Dictionary and be listed. Concomitant medications taken within 28 days post each vaccination, and analgesic or antipyretic medications taken within 7 days post each vaccination will be summarized. The summaries will be presented by treatment group as defined in Section 5 for subjects in the Safety set.

8.2. Medical and Surgical Procedures

Medical or surgical procedures will be presented in a data listing.

8.3. Study Drug Administration

Study drug administration will be presented in a data listing.

9. Safety Analysis

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

9.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Adverse events will also be evaluated by the investigator for the coexistence of medically attended AE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Adverse events will be coded by preferred term (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group as defined in Section 5, vaccination (first or second), and overall.

All summary tables (except for the overall summary of AEs) will present SOC and PT, will include counts of subjects, and will be based on TEAEs. System organ class will be displayed in descending order of overall frequency and then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. Percentages will be based upon the number of subjects in the Safety set within each treatment group as defined in Section 5.

9.1.1. Incidence of Adverse Events

Individual subject listings will be provided for all AEs, AEs leading to withdrawal, AESIs, medically attended AEs.

An overall summary of AEs will be created to include the number and percentage of subjects who experience the following:

- Any unsolicited AE (Part A)
- Any unsolicited treatment-related AE (Part A)
- Any unsolicited AE of grade 3 or 4 (Part A)
- Any unsolicited treatment-related AE of grade 3 or 4 (Part A)
- Any SAE (Part A)

- Any treatment-related SAE (Part A)
- Death (Part A)
- Any AEs leading to withdrawal (Part A)
- Any AE of special interest (Part A)
- Any medically-attended AE (Part A)
- Any SAE (Part B)
- Any treatment-related SAE (Part B)
- Death (Part B)
- Any AEs leading to withdrawal (Part B)
- Any AE of special interest (Part B)

The AEs in Part A will be the AEs that started on or before Visit 7. The AEs in Part B will be the AEs that started after Visit 7.

9.1.2. Relationship of Adverse Events to Study Drug

The relationship of AEs to the study drug (not related, related) will be captured on the eCRF.

The TEAEs related to study drug will be summarized by treatment groups as defined in Section 5 and overall, as well as by SOC and PT. If the relationship to study vaccine is missing, then a "missing" relationship category will be included in the summary. A subject with 2 or more AEs within the same SOC or PT level but different relationship will be counted only once in the level using the related incident.

9.1.3. Severity of Adverse Event

The severity of AEs (Grade 1, 2, 3, or 4) will be captured on the eCRF. The TEAEs will be summarized by treatment groups as defined in Section 5 and overall, as well as by SOC, PT, and severity. If the severity is missing, then a "missing" severity category will be

included in the summary. A subject with 2 or more AEs within the same SOC or PT level but different severity will be counted only once in that level using the most severe incident.

9.1.4. Serious Adverse Events

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

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

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

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

The SAEs will be presented in a data listing and summarized by treatment groups as defined in Section 5 and overall, as well as by SOC and PT. A subject with 2 or more SAEs within the same level of summarization will be counted only once in that level.

9.1.5. Adverse Events Leading to Withdrawal

The AEs leading to withdrawal will be presented in a data listing.

9.1.6. Adverse Events of Special Interest

Certain AESIs are evaluated after the administration of immunostimulatory agents. All subjects enrolled in the study will be monitored for AESIs from enrollment through the EOS visit. The occurrence of any of these AEs will be treated as an SAE, meeting the criterion of a "medically important event." The list of AESIs is presented in Section 6.2 of the Protocol. The AESI diagnosis, as well as any medications taken to treat the condition, will be recorded in the subject's eCRF.

All AESIs will be presented in a data listing.

9.1.7. Solicited Adverse Events

The term "reactogenicity" refers to selected signs and symptoms occurring after dose administration, to be collected by the subject during the day of each dose administration and for the following 7 days using self-reporting and the memory aid.

The following solicited reactogenicity events are included in the memory aid:

Solicited local reactogenicity events:

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

Solicited systemic reactogenicity events:

- body temperature (oral)
- generalized myalgia (muscle ache or pain)
- generalized arthralgia (joint ache or pain)
- headache

- fatigue/malaise (unusual tiredness)
- nausea/vomiting
- diarrhea

The investigator will later review, confirm, grade, and attribute reactogenicity events, as absent (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4) based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (CBER 2007; Table 6-3 in the protocol).

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

- Solicited local or systemic reactogenicity event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator
- Solicited local or systemic reactogenicity event lasting beyond 7 days duration
- Solicited local or systemic reactogenicity event that lead to subject withdrawal from study drug
- Solicited local or systemic reactogenicity event that otherwise meets the definition of an SAE

The solicited local and systemic reactogenicity events will be presented in the data listings, and be summarized by treatment as defined in Section 5 and overall, vaccination (first or second), day after vaccination (1-7) and severity. The duration of solicited reactogenicity events will be summarized by treatment as defined in Section 5 and overall, and vaccination (first or second).

The solicited reactogenicity events entered as AEs in the AE eCRF page that are related to study drug will be summarized by treatment groups as defined in Section 5 and overall, as well as by SOC and PT. If the relationship is missing, then a “missing” relationship category will be included in the summary. A subject with 2 or more AEs within the same

SOC or PT level but different relationship will be counted only once in the level using the related incident.

9.2. Clinical Laboratory Evaluations

The following hematology, serum chemistry, coagulation, and urinalysis assessments will be performed:

Hematology:	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and total and differential leukocyte count
Serum chemistry:	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, amylase, lipase, bilirubin (total and direct), blood urea nitrogen, creatinine, random glucose, potassium, sodium, total protein, albumin, and calcium
Coagulation:	Prothrombin time, partial thromboplastin time
Urinalysis:	pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, leucocytes, and specific gravity

A pregnancy test (β-human chorionic gonadotropin) will be performed on all female subjects of childbearing potential at Screening and before each dose administration (urine or serum). A follicle-stimulating hormone test will be performed at Screening, as necessary, to confirm post-menopausal status in female subjects, if not documented in the subject's medical records.

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

A urine screen for drugs of abuse will be performed by the local laboratory at Screening for alcohol, opiates, cocaine, phencyclidine, amphetamines, benzodiazepines, and methadone.

All safety values that have a toxicity score of Grade 1 or greater will also be evaluated by the investigator and classified as "abnormal clinically significant (CS)", or "abnormal not

clinically significant (NCS)." Investigators should use their clinical judgment when considering the clinical significance of any abnormal laboratory findings. All laboratory test values with a toxicity score of Grade 3 or greater will be entered as AEs. Any additional laboratory test value that is determined to be clinically significant will also be recorded as an AE, should that be considered the primary diagnosis. In such instances, the abnormal value and grade will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached the reference range or the values at Screening or until the investigator determines that follow-up is no longer medically necessary. The only exception to this rule would be a laboratory test value that is associated with an identified ongoing AE where that event would be the classifying AE.

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 subject has a laboratory test with Grade 2 or higher abnormality at any post vaccination visit, then all results for that subject and laboratory test will be presented in the listing.

For hematology, serum chemistry, coagulation, and numeric urinalysis test results, the observed values and changes from Baseline on Days 7, 17, 28 after each vaccination and for sentinel safety subjects also on Day 21 post first vaccination will be summarized by treatment groups as defined in Section 5. These laboratory tests will also be summarized by the toxicity grades.

9.3. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Vital signs will be measured in Part A at Screening, before and after vaccination on the day of the first vaccination, on Days 1 and 2 (only for sentinel safety subjects), 7, 21 (only for sentinel subjects), and 28 (before second vaccination) post first vaccination, as well as after vaccination on the day of the second vaccination, and on Days 7 and 28 post second vaccination.

If any of the vital sign measurements meet the toxicity grading criteria for clinical abnormalities of Grade 2 or higher, the abnormal value and grade will be documented on

the AE page of the eCRF (unless there is another known cause of the abnormality and that would result in an AE classification).

The vital sign measurements will be presented in a data listing. The values meeting the toxicity grading criteria will be flagged in the data listing. Observed values and changes from Baseline will be summarized by treatment groups as defined in Section 5.

9.4. Physical Examination

In Part A, a full physical examination will be performed at Screening and symptom-directed (targeted) physical examinations will be performed before first vaccination and at Day 7, Day 21 (for sentinel safety subjects only) and Day 28 (before second vaccination) post first vaccination, as well as at Day 7 and 28 post second vaccination. The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Prior to vaccination and at 7 days following vaccination, a physical evaluation of the arm that was vaccinated and the associated lymph nodes should be evaluated.

Physical examination data will be presented in a data listing.

Height and weight will be measured and body mass index will be calculated at Screening only and listed together with the demographic data.

10. Immunogenicity Analysis

The following immunogenicity outcome measures (for serum neutralizing antibody titers and serum binding antibody titers to CHIKV-specific proteins) and their 95% CIs, where appropriate, will be summarized by treatment groups as defined in Section 5, and by time points:

- Geometric mean titer at baseline (pre-vaccination at Visit 1) and at post-dose time points

- Geometric mean ratio $(GMR)_{Post/Pre}$: the ratio of post-vaccination GMT to pre-vaccination (Visit 1) GMT of subjects who have a baseline sample and post-vaccination sample at post-dose time point

- Seroresponse: the proportion of subjects in each treatment group who

    - had an undetectable titer (<LLOQ) at baseline and detectable titer (>=LLOQ) after vaccination

    - had a detectable titer (>=LLOQ) at baseline and at least a 4-fold increase (of baseline titer) after vaccination

    - had titers meeting either of the above conditions (for overall summary)

- Percentages of subjects with antibody titer >= detectable titer (LLOQ) at baseline and each post-vaccination timepoint

- Reverse Cumulative Distribution Function of Serum Antibody Titer Values by time point and treatment group

The immunogenicity analyses will be performed separately for the PP sets and the ITT sets. Part A (Visit 1 through Visit 7) immunogenicity data will be included in the analyses for the Primary PP set and the Primary ITT set. Part B (Visit 12 through Visit 19) immunogenicity data will be included in the analyses for the Persistence PP set and the Persistence ITT set.

An exploratory analysis of serum neutralizing antibody titers will be performed using the PRNT80 assay (in addition to PRNT50 assay that used for secondary objectives).

11. Interim Analysis

Following completion of each dose level cohort in Part A, the database will be locked for that cohort and safety and/or immune testing results through 28 days following the final vaccination will be analyzed. As dose escalation occurs, cumulative analyses will be included for each subsequent data lock to allow for all prior dose level cohorts to be analyzed by dose level and in aggregate for VAL-181388 exposure. Also an interim analysis of safety, reactogenicity immunogenicity data collected from Day 1 to Month 7 will be conducted. Immunogenicity and safety data, including analyses of change from

baseline, where applicable, will be summarized for each dose level cohort and combined placebo group. These analyses will be performed by an unblinded team, independent of the study team. Access to individual listings will be restricted to identified Sponsor members and the clinical research organization unblinded team. Study sites will remain blinded. This analysis will provide information regarding short-term antibody persistence.

12. References

Akahata W, Yang ZY, Andersen H, et al. A virus-like particle vaccine for epidemic chikungunya virus protects nonhuman primates against infection. Nat Med. 2010;16(3):334-8.

Brandler S, Ruffie C, Combredet C, et al. A recombinant measles vaccine expressing chikungunya virus-like particles is strongly immunogenic and protects mice from lethal challenge with chikungunya virus. Vaccine. 2013;31(36):3718-25.

Centers for Disease Control and Prevention. Chikungunya virus geographic distribution [updated 22 Apr 2016; cited 2016 Sep 09]. Available from: http://www.cdc.gov/chikungunya/geo/index.html.

Darwin JR, Kenney JL, Weaver, SC. Transmission potential of two chimeric Chikungunya vaccine candidates in the urban mosquito vectors, Aedes aegypti and Ae. Albopictus. Am J Trop Med Hyg. 2011;85(6):1012-5.

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13. Schedule of Events

The schedule of events for Part A is presented in Table 13-1 and the schedule of events for Part B is presented in **Error! Reference source not found.**.

Table 13-1 Part A: Schedule of Events

Procedure	**Screening**	**Treatment Period**									
Study visit	**0**	**1**	**1a[a]**	**1b[a]**	**2**	**3**	**3a[a]**	**4**	**5**	**6**	**7**
Vaccination Day		**X**						**X**			
Days relative to most recent vaccination	**N/A**	**0**	**1**	**2**	**7**	**17**	**21**	**28**	**7**	**17**	**28**
Window allowance	**+28**	**0**	**0**	**0**	**+3**	**±3**	**+3**	**+7**	**+3**	**±3**	**+7**
Informed consent	X										
Inclusion/exclusion criteria	X										
Medical history	X										
Physical examination[b]	X	X[c]			X		X	X[c]	X		X
Vital sign measurements[d]	X	X[c]	X	X	X		X	X[c]	X		X
Serology[f]	X										
Clinical laboratory testing	X[g]	X[c,g]			X[g]	X[h]	X[h]	X[c,g]	X[g]	X[h]	X[h]
Urine drug screen[i]	X										
Pregnancy test (female subjects of childbearing potential)	X	X[c]						X[c]			
Follicle-stimulating hormone (female subjects only)[j]	X										
Randomization		X									
Blood sample for serum neutralizing antibody titers[k]		X[c]						X[c]			X
Blood sample for serum antibody titers to CHIKV protein[k]		X[c]						X[c]			X
Blood sample for exploratory antibody assay[k]		X[c]						X[c]			X
Study drug administration		X						X			
Reactogenicity		X[c]	X	X	X		X	X[c]	X		X
Subject memory aid completion: solicited local and systemic AEs, oral body temperature, and medications taken[l]		X Visit 1 through Visit 2						X Visit 4 through Visit 5			
Subject memory aid completion: any unsolicited AEs and related medications[l]		X Visit 1 through Visit 7									

Procedure	**Screening**	**Treatment Period**									
Study visit	**0**	**1**	**1a[a]**	**1b[a]**	**2**	**3**	**3a[a]**	**4**	**5**	**6**	**7**
Vaccination Day		**X**						**X**			
Days relative to most recent vaccination	**N/A**	**0**	**1**	**2**	**7**	**17**	**21**	**28**	**7**	**17**	**28**
Window allowance	**+28**	**0**	**0**	**0**	**+3**	**±3**	**+3**	**+7**	**+3**	**±3**	**+7**
Collection of memory aid								X			X
Adverse events assessment[m]	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications[n]	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CHIKV, chikungunya virus; NA, not applicable.

a. This visit is required for sentinel safety group subjects only.
b. Full physical examination at Screening; symptom-directed (targeted) physical examination at all other scheduled time points. Interim physical examinations will be performed at the discretion of the investigator, if necessary. Height and weight will be measured and body mass index calculated at Screening only.
c. Assessment to be performed before study drug administration.
d. Vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) on Visits 1 and 4 will be collected once before study drug administration and at least 1 hour after study drug administration (before subjects are discharged). Vaccination cannot occur if systolic or diastolic blood pressure, heart rate, or respiratory rate measurements show Grade 2 or higher toxicity after 2 measurements; if a subject has an acute illness; or if a subject has an oral temperature >38°C.
e. Assessment to be performed before and after study drug administration.
f. Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus type 1 and 2 antibodies.
g. Hematology, serum chemistry, coagulation, and urinalysis assessments.
h. Safety laboratory tests for albumin, bilirubin (total and direct), prothrombin time, partial thromboplastin time, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase.
i. The drug screen will include alcohol, opiates, cocaine, phencyclidine, amphetamines, benzodiazepines, and methadone.
j. To confirm post-menopausal status, as needed.
k. Excess serum from immunogenicity may be used for future research at the discretion of the Sponsor to better characterize the immune response to the CHIKV protein.
l. Subjects will be instructed on how to complete the memory aid prior to discharge from the clinic at Visit 1. Subjects will be instructed to call or return to the clinic within 24 hours if reactogenicity reaches Grade 3 or higher during the first 7 days following vaccination.
m. Adverse events will be assessed from the time of study drug administration on Visit 1 through Visit 7. However, for the time period after the informed consent form is signed until before receiving the study drug, AEs will only be recorded when they are defined as one or more of the following: serious AEs, AEs of special interest, AEs leading to study withdrawal.

n. Prior medications taken by the subject within the 30 days before providing informed consent will be collected. Concomitant medications include all medications (including vaccinations outside of the trial) taken by the subject from the time of signing the informed consent and through Visit 7.

Table 13-2 Part B: Schedule of Events

Procedure												
Study visit[a]	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19[a]**
Study day from 1st dose, if 2nd dose not completed	84	112	140	168	196	224	252	280	308	336	364	392
Study day from 2nd dose, if completed	56	84	112	140	168	196	224	252	280	308	336	364
Window allowance	±7	±7	±7	±7	±15	±7	±7	±7	±7	±7	±7	+15
Type of visit	SC	SC	SC	SC	LV[b]	SC	SC	SC	SC	SC	SC	LV[b]
Safety contact[c]	X	X	X	X		X	X	X	X	X	X	
Blood sample for serum neutralizing antibody titers[d]					X							X
Blood sample for serum antibody titers to CHIKV proteins[d]					X							X
Blood sample for exploratory antibody assays[d]					X							X
Adverse events assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[f]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CHIKV, chikungunya virus; LV, laboratory visit; SC; safety contact.

a Visit 19 will be considered the end of study visit.

b Blood samples for immune persistence will be collected from each subject using a method that maintains the blind (eg, home visits, locally contracted laboratories).

c Each safety contact will occur by telemedicine (eg, telephone, text message, internet).

d Excess serum from immunogenicity may be used for future research at the discretion of the Sponsor to better characterize the immune response to the CHIKV protein and/or to assess for cross-reactive antibody responses to other related viruses.

e Each safety contact will capture outcomes of any adverse event of special interest or serious adverse event that remains unresolved since the last visit or is newly identified through scripted query. Additional data may be requested through medically attended visits, and medications and vaccination will be recorded as part of the medical intake for each telemedicine visit.

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