Dynavax Technologies Corporation

STATISTICAL ANALYSIS PLAN

Protocol Title:	Phase 2, Randomized, Active-Controlled, Observer-Blinded, Multicenter Trial of the Immunogenicity, Safety, and Tolerability of rF1V Vaccine with CpG 1018 Compared with rF1V Vaccine in Adults 18 to 55 Years of Age
Protocol Identifier:	DV2-PLG-01
Phase	Phase 2
Investigational Product:	rF1V Vaccine with CpG 1018
Sponsor:	Dynavax Technologies Corporation 2100 Powell Street, Suite 720 Emeryville, CA 94608 U.S.A.

Original Version:	Version 1: 27 July 2022
Amendment 1:	Version 2: 01 April 2024
Amendment 2:	Version 2.1: 16 June 2024
Based on Protocol Version:	Amendment 5: 11 August 2023

FINAL STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Definition
AE	adverse event
AESI	adverse event of special interest
AMI	acute myocardial infarction
ATC	anatomical therapeutic chemical
CI	confidence interval
DBL	database lock
eCRF	electronic case report form
EOS	End of Study (visit)
GMC	geometric mean concentration
MedDRA	Medical Dictionary for Regulatory Activities
(MedDRA) PT	preferred term
(MedDRA) SOC	system of organ class
mITT	modified intend-to-treat
PIR	post-injection reaction
PP	per-protocol
SAE	serious adverse event
SD	standard deviation
TE(AE)	treatment emergent (AE)
TFL	tables, figures, listings
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the safety and immunogenicity in healthy adults as described in Protocol DV2-PLG-01 (Amendment 5: 11 August 2023): "Phase 2, Randomized, Active-Controlled, Observer-Blinded, Multicenter Trial of the Immunogenicity, Safety, and Tolerability of rF1V Vaccine with CpG 1018 Compared with rF1V Vaccine in Adults 18 to 55 Years of Age".

2.0 STUDY OVERVIEW

This is a phase 2, randomized, active-controlled, observer-blinded, multicenter trial of the immunogenicity, safety, and tolerability of rF1V vaccine with CpG 1018 compared with rF1V vaccine alone in adults. Approximately two hundred healthy adults 18 to 55 years of age will be enrolled to compare a two-dose regimen of rF1V with CpG 1018 administered on study Days [redacted] with a three-dose regimen of rF1V vaccine alone administered on [redacted].

The study will be conducted in 2 parts (Part 1 and Part 2). The table below outlines study drug administration in both parts. When investigational product is co-administered as 2 separate injections, the injections should be administered in close physical proximity to each other (within approximately 1 inch).

Injections will be administered by study personnel not otherwise involved in the subjects' safety evaluation. Recording and evaluation of safety information and laboratory data will be performed by observers blinded to the subjects' treatment assignment.

Part 1:

There will be 2 methods of rF1V vaccine with CpG 1018 administration:

- Group 1 (N = approximately 20): rF1V vaccine and CpG 1018 will be co-administered as 2 separate injections on Days 1[redacted].
- Group 2 (N = approximately 20): bedside mix of rF1V vaccine + CpG 1018 (administered as 1 injection) and placebo will be administered as 2 separate injections on [redacted]

In addition, rFIV vaccine will be administered alone without CpG 1018:

- Group 3 (N=20): rF1V vaccine and placebo will be administered as 2 separate injections on Days [redacted]

All Groups will receive 2 injections at each treatment visit to maintain the blind.

Part 2: Part 2 will begin after immunogenicity assessments from the [redacted] visit in Part 1 are completed. The method of vaccine administration method that is selected from Part 1 will be evaluated in Part 2.

- Group 1 (if selected) (N=70): rF1V vaccine co-administered with CpG 1018
- Group 3 (N=70): rF1V vaccine co-administered with placebo

OR

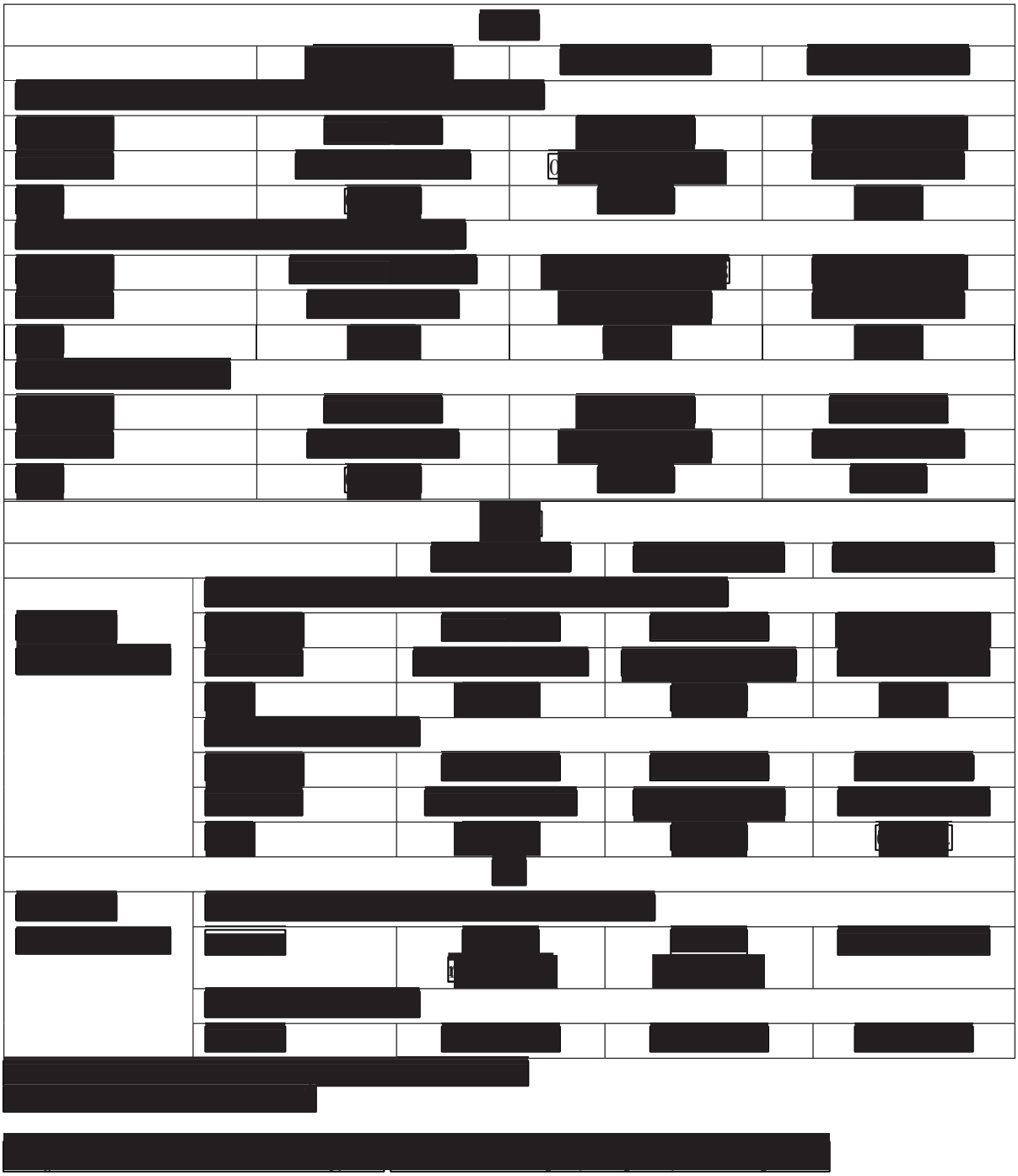
- Group 2 (if selected) (N = 70): bedside mix of rF1V vaccine and CpG 1018
- Group 3 (N=70): rF1V vaccine

Subjects will be followed through Day 393 (Week 56)

The total duration of participation in the Screening, Treatment, and Follow-up parts of this study is up to approximately 60 weeks. This includes a Screening period beginning up to 4 weeks prior to the first study injection and End of Study (EOS) visit 56 weeks after the first study injection.

Study treatments are presented in Table 2-1. For each dose, injections are to be administered in the order specified in the table.

Table 2-1 [redacted]



3.0 STUDY OBJECTIVES AND ANALYSIS VARIABLES

Objectives	Endpoints
PART 1	
Primary	
• To select one of the two methods of administration of rF1V vaccine with CpG 1018 for Part 2 by comparing humoral immunization response 28 days after the second dose of vaccine	• Ratio of geometric mean ELISA concentration (GMC) between rF1V vaccine with CpG 1018 and rF1V vaccine
Secondary	
• To assess the safety and tolerability of rF1V vaccine with CpG 1018 compared with rF1V vaccine	• Rate of reactogenicity: solicited local and systemic post-injection reactions • Rate of adverse events (AEs), severe AEs, serious adverse events (SAEs), immune-mediated adverse events of special interest (AESI), and deaths
PART 2	
Primary	
• To assess the utility of a 2-dose schedule of rF1V vaccine with CpG 1018 as measured by reduction in time to onset of predicted rF1V protection	• Predicted protection (percentage of subjects reaching the [redacted] threshold that corresponds to 50% predicted vaccine efficacy) after 2 doses of rF1V vaccine with CpG 1018 compared to that of 3 doses of rF1V vaccine **Criterion for evaluation**: Similar percentage of subjects reaching the Bridg [redacted]reshold that corresponds to 50% predicted vaccine efficacy after 2 doses of rF1V vaccine with CpG 1018 at [redacted] compared to that after 3 doses of rF1V vaccine [redacted]
• To assess the [redacted] antibody concentration to rF1V with CpG 1018 compared with rF1V vaccine 28 days after the second dose of vaccine	• Ratio of geometric mean ELISA concentration (GMC) between rF1V vaccine with CpG 1018 and rF1V vaccine 28 days after the second dose **Criterion for evaluation**: 2-times increase in [redacted] GMC point estimate after the second dose of rF1V vaccine with CpG

	1018 to that after the second dose of rF1V vaccine at [redacted]
Secondary	
• To assess the safety and tolerability of rF1V vaccine with CpG 1018 compared with rF1V vaccine	• Rate of reactogenicity: solicited local and systemic post-injection reactions • Rate of AEs, severe AEs, SAEs, AESIs, and deaths
• To assess the serum [redacted] concentration to rF1V with CpG 1018 at selected time points after each dose	• GMC and seroconversion rate of serum rF1V [redacted] titers at the following selected time points after each dose of vaccine: [redacted] Seroconversion is defined as the presence of detectable antibody in subjects who had no detectable antibody levels at Day 1, or a 2: 2-fold increase in antibody level in subjects who had detectable antibody levels at Day 1.

	Criterion for evaluation: GMC and seroconversion rate point estimates from rF1V vaccine with CpG 1018 to meet or exceed results from rF1V vaccine at relevant visits

[redacted]

(Days 57, 85, 113 / Weeks 8, 12, 16) as

relevant visits

4.0 SAMPLE SIZE CONSIDERATIONS

Part 2 primary objective 1 is to assess the utility of a 2-dose schedule of rF1V vaccine with CpG 1018 as measured by reduction in time to onset of predicted rF1V protection. The predicted protection will be based on a [redacted]ter threshold. Previous animal studies have established protective efficacy in animals. Since a human efficacy study is not feasible, an immunobridge from animal data to human data via the [redacted] test will be used to predict the protective efficacy in humans using a regression model. An initial predicted protection threshold will be calculated based on the data generated in this study in Group 3 after 3 doses of rF1V vaccine. Once the threshold is identified, it will be applied to the study groups to evaluate the Part 2 objectives. In addition to the previous animal studies conducted to establish protective efficacy, a new animal model utilizing rF1V vaccine with CpG 1018 will be developed to establish the protective level of antibody for CpG 1018 containing vaccines. Additional analyses will include a predicted protection threshold that will be calculated based on the data generated under the new animal model after 2 doses of rF1V vaccine with CpG 1018. In both instances, the animal-to-human immunobridge and the identification of the predicted protection thresholds will be documented in a separate report.

A similar approach was used to analyze the previous Phase 2a (NCT00332956) and Phase 2b (NCT01122784) study data using the animal model from the previous animal studies. Thresholds that corresponded to 50% predicted protective efficacy in humans were established for those trials. In a pooled analysis of these previous immunobridge studies, 93% (95% Clopper Pearson confidence interval [CI] = 85%, 98%) of subjects reached the predicted protection threshold.

It is assumed that a similar percentage of the subjects in Group 3 will reach the threshold identified in this study. When this threshold is applied to both Part 2 study groups, a similar lower bound of the 95% CI is desired across the groups. Table 4-1 shows the lower bound of 95% Clopper Pearson CI for different observed levels of predicted protection assuming 85 of the 90 planned subjects (Part 1 N = 20 and Part 2 N =70) will have data available for the evaluation. Thus, with a predicted protection level of 93%, the lower bound of the 95% CI would be 85%.

Table 4-1: Precision Estimate at Various Level of Predicted Protection Using Clopper Pearson CI (N=85)

Predicted Protection Level	Lower Bound of 95% CI	Upper Bound of 95% CI
95%	88%	99%
93%	85%	97%
91%	82%	96%

When the lower bound of 95% CI for the predicted protection after 2 doses of rF1V vaccine with CpG 1018 (ie, at Week 8) is similar to that after 3 doses of rF1V vaccine (ie, at Week 30), the reduction of onset time to predicted rF1V protection is demonstrated.

5.0 ANALYSIS POPULATIONS

5.1 Enrolled Population

The enrolled population is defined as all subjects who enrolled in the study.

5.2 Safety Population

The Safety Population will comprise all subjects who receive at least 1 dose of the study vaccine, excluding subjects who have no on-study data.

5.3 Immunogenicity Population

The modified intent-to-treat (mITT) population will comprise all eligible subjects who received at least 1 dose of study vaccine and have a post-injection immunogenicity evaluation.

The per-protocol (PP) population for the immunogenicity analyses will comprise Groups 1 and 2 subjects who received 2 doses of study vaccine and Group 3 subjects who received 3 doses of study vaccine, have no major protocol deviations (see Section 8.2), and have immunogenicity data obtained within the study visit window at Day [redacted] for Groups 1 and 2 and Day [redacted] for Group 3.

Note: the PP population definition and major protocol deviations in Section 8.2 are updated from the Protocol Amendment 5.

6.0 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

6.1 Definitions and Computations

Study Day

Study day will be calculated in reference to the date of first injection (Day 1). For visits conducted on or after the first injection date, study day is calculated as (visit date – first injection date + 1). For visits conducted before the first injection date, study day is calculated as (visit date – first injection date). There will be no Day 0.

Date of First Injection and Date of Last Injection of Study Vaccine

The date of the first injection of study vaccine is defined as the date a subject receives the first injection of the study vaccine. The date of the last injection of study vaccine is the date a subject receives the last injection of the study vaccine.

Treatment-Emergent Period

The reporting period for all non-serious AEs begins at the time of the first study injection (Day 1) through EOS Visit. All AEs will be captured on the AE eCRF.

Any SAE that occurs from the time the consent is signed through EOS Visit, whether or not the SAE is related to the study treatment, must be reported.

The treatment-emergent (TE) period is defined as time from the first study injection through EOS Visit.

6.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Age will be calculated by the following SAS code:

  If only year of birth is given, then Age = (Year of Screening – Year of Birth). Otherwise

  ```
  age = floor ((intck('month', birth_date, consent_date) -
  (day(consent_date) < day(birth_date))) / 12);
  ```

- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- Temperature will be converted from Fahrenheit to Celsius using the following formula: (temperature°F - 32) x 5/9
- Missing safety data will not be imputed unless otherwise specified.
- For immunogenicity results, the [redacted]concentrations are obtained using the ELISA assay. For concentration reported as <value, half of the value will be used in calculation. For concentration reported as >value, value+1 will be used in calculation.
- For unsolicited safety analyses, percentages will be calculated based on the number of subjects in the analysis population.
- For by-visit observed data analyses, percentages will be calculated based on the number of subjects with nonmissing data as the denominator unless otherwise specified.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include counts and percentages.

- AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher.
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version 202009 or higher.

6.3 Rules for Missing Data

Missing data will not be imputed, except for missing date information for AEs and concomitant medications. The imputed dates will be used to determine the treatment-emergent period. For AEs with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the AE will be considered treatment emergent by default.
The following rules will be applied to impute partial dates for AEs:

- If start date of an AE is completely or partially missing, impute as follows:
  - If both month and day are missing and year = year of first dose date, then set to first dose date.
  - If both month and day are missing and year i- year of first dose date, then set to January 1.
  - If day is missing and month and year = month and year of first dose date, then set to first dose date.
  - If day is missing and month and year i- month and year of first dose date, then set to first of the month.
  - If start date is completely missing and AE end date is on or after the first dose date, set to first dose date.
  - If start date is completely missing and AE end date is prior to the first dose date, do not impute an AE start date.
- If end date of an AE is partially missing, impute as follows:
  - If both month and day are missing, then set to December 31.
  - If only day is missing, then set to last day of the month.
  - If end date is completely missing, do not impute.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to January 1.

  - If only day is missing, then set to the first of the month.
- If end date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to December 31.
  - If only day is missing, then set to last day of the month.
- If start date or end date of a medication is completely missing, do not impute.

Listings will show the original date information without imputation, but derived parameters (TEAE indicator and duration of AE) will be flagged to indicate the type of imputation performed.

7.0 TIMING OF ANALYSES

The administration method of vaccine utilized in Part 2 of the study will be selected by Dynavax in consultation with the Department of Defense (DoD) after Day 57 immunogenicity data in Part 1 subjects become available. The evaluation will be based on unblinded data. Blinding will be retained for those who are blinded per study requirements throughout the study.

Final analyses will be carried out after the last participant has completed their last study visit, the study database has been authorized by Dynavax as complete and final, and major protocol deviations have been identified.

8.0 STATISTICAL METHODS

This is a phase 2, randomized, active-controlled, observer-blinded, multicenter trial of the immunogenicity, safety, and tolerability of rF1V vaccine with CpG 1018 compared with rF1V vaccine alone in adults.

Part 1 objectives will be evaluated descriptively. The administration method of vaccine utilized in Part 2 of the study will be selected by Dynavax in consultation with the Department of Defense (DoD) after Day 57 immunogenicity data become available to determine whether the GMC 1 month after 2 doses of rF1V vaccine with CpG 1018 using the selected administration method is at least 2 times higher than that 4 weeks after 2 doses of rF1V vaccine in Group 3.

The proposed statistical planning for Part 2 is presented according to the objectives. Data from Part 1 and Part 2 will be combined to evaluate the Part 2 objectives. No multiplicity adjustments are made, and all statistical tests will be conducted at 5% two-sided Type I level unless otherwise specified. All confidence intervals are two-sided 95% confidence intervals unless otherwise specified.

All analyses of demographics and baseline characteristics, medical history, vaccine exposure and safety will be summarized in a descriptive manner. In general, continuous variables will

be summarized by number of subjects, mean, standard deviation, median, quartiles, minimum and maximum, and categorical variables will be summarized by number and percentage of subjects in each study group as appropriate. All data processing, summarization, and analyses will be performed using SAS Version 9.4 or higher. Specifications for tables, graphs, and data listings will be provided in the tables, figures, listings (TFL) specifications document as needed. No specific safety hypotheses will be tested.

8.1 Subject Disposition

Subject disposition will be summarized for all enrolled subjects including subjects in the safety, PP and mITT populations and subjects discontinuing the study along with the reasons for discontinuation (as documented on the case report form Study Completion).

A listing of subjects discontinuing the study after enrollment will be produced.

8.2 Protocol Deviations

For the purpose of selecting subjects for the per-protocol population, a major protocol deviation is defined as one of the following:

- not meeting one or more enrollment criteria,
- vaccine was not given per-protocol,
- [redacted] serum sample obtained outside protocol specified visit window 4 weeks following the second study injection for rF1V vaccine with CpG 1018 groups ([redacted]) and the third study injection for rF1V vaccine only group ([redacted]). This deviation will be identified at both visits, but will be applied for each group by corresponding visit for exclusion purpose post database lock (DBL), as this deviation is dependent upon treatment assignment for complete adjudication, e.g. a subject who was vaccinated per protocol but who had the Day [redacted] blood sample drawn out of window, is marked as a major protocol deviation. Following DBL and unblinding, if the subject is found to be in the rF1V vaccine with CpG-1018 group, although the out of window of the sample is considered a major protocol deviation, the subject will be included in the per protocol analysis set provided no other major protocol deviations apply.
- received prohibited concomitant medications.

The following non-study medications are prohibited for the purpose of evaluating per-protocol population:

- Any licensed COVID-19 vaccine or inactivated vaccine (including vaccines containing mRNA or CpG)
  - :S 14 days prior to each study injection through 14 days after each study injection
- Any live vaccine
  - :S 28 days prior to each study injection through 28 days after each study injection
- Other concomitant medications

- :S 28 days prior to vaccine injection (Day 1) through 28 days after the third study vaccine injection [redacted]
  - Systemic corticosteroids (more than 3 consecutive days) or other immunomodulators or immunomodulators immune suppressive medication, with the exception of inhaled steroids
  - Any other investigational medicinal agent
- :S 90 days prior to vaccine injection (Day 1) and through 28 days after the third study vaccine injection [redacted]
  - Granulocyte or granulocyte-macrophage colony-stimulating factor
  - Immunoglobulins or any blood products
  - Antisense oligonucleotides
  - Drugs/investigational agents with very long half-lives (defined as 2: 60 days)
- At any time prior to vaccine injection (Day 1) and through 28 days after the third study vaccine injection [redacted]
  - DNA plasmids or other genetic therapy intended to integrate permanently into host cells

A listing of subjects with major protocol deviations will be provided describing their deviations. Any exclusions from analysis populations due to protocol deviations and other reasons will also be listed.

8.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed by subject and summarized using the Safety Population. Descriptive summary statistics (sample size, mean, median, SD, and range, when appropriate) will be provided for the continuous variables such as age, weight, and height. Count and percentage will be reported for categorical variables such as sex, race, and ethnicity.

Listings will be provided for these parameters for all subjects.

8.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications are drugs and therapies used before the first dose date. Medications or therapies are considered concomitant if exposure occurs after the first dose date. The number and percentage of subjects with concomitant medications will be presented alphabetically by anatomical therapeutic chemical (ATC) class and by decreasing order of frequency of preferred terms within each ATC class for the safety population. Subjects taking the same medication multiple times will be counted once per medication.

All medications recorded on the case report form will be listed.

8.5 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities. Medical history will be summarized by System of Organ Class (SOC) and Preferred Term (PT) for safety population. All medical history data will be provided in a listing.

8.6 Immunogenicity Analyses

The primary and other immunogenicity endpoints will be analyzed using the mITT population. Sensitivity analyses on immunogenicity data will also be presented using the PP population.

Immunogenicity will be measured by serum rF1V [redacted] concentration at each visit.

Data from Part 1 subjects and Part 2 subjects will be combined to evaluate the Part 2 objectives. No multiplicity adjustment is proposed.

Additional analyses may be attempted, including analysis to quantify antibody decay over time.

Part 1 Primary Objective: To select one of the two methods of administration of rF1V vaccine with CpG 1018 for Part 2 by comparing humoral immunization response 28 days after the second dose of vaccine

Endpoint: Ratio of geometric mean ELISA concentrations (GMCs) between rF1V vaccine with CpG 1018 and rF1V vaccine.

Estimand: GMCs and associated two-sided 95% confidence intervals for each of the 3 study groups will be computed by exponentiating the mean and associated Student's t confidence interval of the log10 transformed individual antibody concentrations assuming Normal distribution. The ratio of GMCs and associated two-sided 95% confidence interval will be compared between rF1V vaccine with CpG 1018 and rF1V vaccine, using Student's t method. The ratio of GMCs and associated two-sided 95% confidence interval between two administration methods of rF1V vaccine with CpG 1018 vaccines will also be produced.

Criterion for evaluation: GMC 1 month after 2 doses of rF1V vaccine with CpG 1018 using the selected administration method is at least 2 times higher than that 4 weeks after 2 doses of rF1V vaccine.

Part 2 Primary Objective 1: To assess the utility of a 2-dose schedule of rF1V vaccine with CpG 1018 as measured by reduction in time to onset of predicted rF1V protection

Endpoint: Predicted protection (percentage of subjects reaching the [redacted] threshold that corresponds to 50% predicted vaccine efficacy) at Week [redacted] after 2 doses of rF1V vaccine with CpG 1018 as that at Week [redacted] after 3 doses of rF1V vaccine without CpG 1018. The [redacted] threshold that corresponds to 50% predicted vaccine efficacy will be obtained from a model using [redacted] data after 3 doses of rF1V vaccine (or after 2 doses of rF1V

with CpG 1018 TBD) in this study. The threshold and the model used will be described in a separate report. Part 2 Primary Objective 1 can only be evaluated after the determination of this threshold.

Estimand: Percentage of subjects reaching the [redacted] threshold and associated 95% two-sided Clopper-Pearson confidence intervals will be computed. Fisher's exact tests will be used to compare predicted protection rate between study groups.

Criterion for evaluation: Similar percentage of subjects reaching the [redacted] threshold that corresponds to 50% predicted vaccine efficacy after 2 doses of rF1V vaccine with CpG 1018 as compared to that after 3 doses of rF1V vaccine.

Part 2 Primary Objective 2: To assess the serum [redacted] concentration to rF1V vaccine with CpG 1018 compared with rF1V vaccine 28 days after the second dose of vaccine

Endpoint: Ratio of geometric mean ELISA concentration (GMC) between rF1V vaccine with CpG 1018 and rF1V vaccine at Week [redacted].

Estimand: GMCs and associated two-sided 95% confidence intervals will be computed by exponentiating the mean and associated Student's t confidence interval of the log10 transformed individual antibody concentrations assuming Normal distribution. The ratio of GMCs and associated two-sided 95% confidence interval will be compared between rF1V vaccine with CpG 1018 and rF1V vaccine, using ANOVA if site can be used as an adjustment factor in the model or Student's t method.

Criterion for evaluation: 2-times increase in [redacted] GMC point estimate after the second dose of rF1V vaccine with CpG 1018 to that after the second dose of rF1V vaccine.

Part 2 Secondary Objective: To assess the serum [redacted] concentration to rF1V with CpG 1018 at selected time points after each dose

Endpoint: GMC and seroconversion rate of serum rF1V [redacted] titers at the following selected time points after each dose of vaccine:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

Seroconversion is defined as the presence of detectable antibody in subjects who had no detectable antibody levels at Day 1, or a 2: 2-fold increase in antibody level in subjects who had detectable antibody levels at Day 1.

Estimand: GMCs and associated two-sided 95% confidence intervals will be computed by exponentiating the mean and associated Student's t confidence interval of the log10 transformed individual antibody concentrations assuming Normal distribution. Seroconversion rate and associated 95% two-sided Clopper-Pearson confidence intervals will be computed.

Criteria for evaluation: GMC and seroconversion rate point estimates from rF1V vaccine with CpG 1018 to meet or exceed results from rF1V vaccine at relevant visits.

Part 2 Exploratory Objective 1: [redacted]

[redacted]

8.7 Safety Analyses

Vaccine exposure and compliance will be summarized descriptively for safety population.

Safety data will be analyzed descriptively and will be based on the safety population. The safety parameters will be presented for all sites combined. Summary statistics will be used to describe the incidence of all post-injection reactions (PIRs) and AEs, including SAEs, deaths, acute myocardial infarctions (AMIs), and AESIs. AMIs include the events with PTs of Acute Myocardial Infarction, Acute Coronary Syndrome, or Myocardial Infarction. The incidence and proportion of post-injection reactions and AEs will be summarized. AEs will be coded using the MedDRA SOC and PT.

The treatment-emergent period is defined in Section 6.1.

On Day [redacted] Day [redacted], and Day [redacted], subjects will be asked to complete an e-diary (or equivalent) to record any solicited local and systemic reactions during the 7-day follow-up period after vaccination. Post-injection reactions persisting beyond 7 days after injection are considered to be AEs and need to be recorded and reported as AEs (see protocol Section 10.2). The severity of the post-injection reactions will be graded using the United States Food and Drug Administration's (FDA) Guidance for Industry: Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Local reactions include pain, redness, pruritus and swelling, and systemic reactions include fatigue, temperature, chills, malaise, myalgia, vomiting, diarrhea, and headache.

Post-injection reactions reported from day 1 to day 7 will be summarized by maximal severity and by vaccine group. The severity of local reactions, including redness and swelling will be categorized as none (:S25mm), >25 to :S50mm (mild), >50 to :S100mm (moderate) and >100mm (severe).

The severity of local reactions including pain, and pruritus and systemic reactions including fatigue, chills, malaise, myalgia, vomiting, diarrhea and headache occurring up to 7 days after each vaccination will be categorized as none, mild (no interference with activity), moderate (some interference with activity), severe (significant, prevents daily activity).

Temperature will be categorized as <38°C (no fever), 38-38.4°C (mild), 38.5-38.9°C (moderate), 39-40°C (severe) and >40°C (life threatening).

Each local and systemic reaction will also be categorized as none vs. any.

All AEs will be coded to preferred term and system organ class. An AE that started or increased in severity during the treatment-emergent period will be considered a TEAE. The severity of AEs and laboratory abnormalities will be graded based on CBER Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, with the modification that, by convention, all fatal AEs will be graded as Grade 5 (Fatal). All AEs not listed in the CBER toxicity grading scale will be graded as shown in Table 8-1.

Table 8-1: Grading Scale for Adverse Events Not Included in the CBER Guidance on Toxicity Grading for Healthy Volunteers in Vaccine Clinical Trials

AE Severity	Definition
Grade 1 – Mild	No interference with activity
Grade 2 – Moderate	Some interference with activity, not requiring medical intervention

AE Severity	Definition
Grade 3 – Severe	Prevents daily activity and requires medical intervention
Grade 4 – Potentially life-threatening	Emergency room visit or hospitalization
Grade 5	Death

A study vaccine -related TEAE is defined as any TEAE with at least a possible relationship to the study vaccine as assessed by the investigator.

Subjects with multiple occurrences of events for a given preferred term, system organ class, or overall will only be counted once at the worst severity and strongest relationship to study vaccine for each PT, SOC, and overall, respectively. AEs that are continuous but change in grade, relationship, or seriousness will be counted as 1 event. TEAEs of unknown severity will be categorized separately. A TEAE of unknown relationship will be categorized separately.

Incidences and percentages of subjects experiencing each reaction will be presented by severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

Tabular summaries including numbers and percentages of the following adverse events will be provided:

- All TEAEs
- TEAEs of Grade 3 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- All treatment-emergent SAEs
- All treatment-related SAEs
- All TEAEs leading to premature discontinuation of study vaccine
- All SAEs leading to death
- All AMI
- All AESI

Listings will be provided for all TEAEs.

8.8 Other Analyses

No other analyses are planned.

8.9 Interim Analysis

This study has no planned interim analysis.

8.10 Reporting Output

All outputs will be produced using SAS® Version 9.4 or later. The REPORT procedure will be used to produce all tables and listings whenever possible. The SGPLOT procedure will be used to produce all figures whenever possible. All statistical appendices (supportive SAS output) will be output directly from the appropriate SAS procedure.

Post-text tables, listings, and statistical appendices will be produced as RTF files using output delivery system (ODS) and Times New Roman or a similar font size 8 or larger. Data will be presented in RTF tables with data in individual cells. Figures will be produced as RTF files using ODS and simplex font. For all outputs, the page numbering will be applied to ensure that when the RTF files are combined, the page numbering remains fixed.

All tables, listings and statistical appendices will be produced to landscape orientation and will be incorporated into a Word 2010 or later document (margins: top 1.5”, left, right and bottom 1”) using 8pt font or larger.

Vaccine name for tables and figures will be as follows:

Group	Vaccine Name
Group 1	rF1V+1018 CO
Group 2	rF1V+1018 BM
Group 3	rF1V Only

9.0 REVISION HISTORY

Version	Date	Author	Comments/Rationale for Revision
1.0	27JUL2022	[redacted]	New Document
2.0	01APR2024	[redacted]	Amendment to incorporate changes in protocol Amendments 4 and 5 including update of PP population definition and addition of objectives of rF1 and rV antibody responses
2.1	xxJUN2024	[redacted]	Clarify PP population definition in Protocol

10.0 REFERENCES

None

11.0 LIST OF TABLES

List of tables will be provided in a separate Table of Contents of Tables, Figures and Listings document.

12.0 LIST OF FIGURES

List of figures will be provided in a separate Table of Contents of Tables, Figures and Listings document.

13.0 LIST OF SUBJECT DATA LISTINGS

List of listings will be provided in a separate Table of Contents of Tables, Figures and Listings document.