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 No.:	DV2-PLG-01
Investigational Product:	rF1V Vaccine with CpG 1018
Study Phase:	2
US IND Number:	028166
Sponsor:	Dynavax Technologies Corporation 2100 Powell Street, Suite 720 Emeryville, CA 94608 U.S.A

Original Protocol:	07 March 2022
Amendment 1:	11May 2022
Amendment 2:	01 June 2022
Amendment 3:	06 June 2022
Amendment 4	07 December 2022
Amendment 5	11 August 2023

This study will be conducted in accordance with good clinical practice (GCP) as defined in International Council for Harmonisation (ICH) Guidelines E6 (R2) and applicable local legal and regulatory requirements.

PROTOCOL APPROVAL PAGE

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 No.: DV2-PLG-01

Amendment 5: 11 August 2023

Sponsor: Dynavax Technologies Corporation
2100 Powell Street, Suite 720 Emeryville, CA 94608
U.S.A.

This protocol has been approved by Dynavax Technologies Corporation. The following signature documents this approval.

[redacted]

INVESTIGATOR SIGNATURE PAGE

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 No.: DV2-PLG-01

Amendment 5: 11 August 2023

Sponsor: Dynavax Technologies Corporation
2100 Powell Street, Suite 720
Emeryville, CA 94608
U.S.A.

DECLARATION OF INVESTIGATOR

I confirm that I have read and understood this protocol and agree to conduct the study as outlined in the protocol and other information supplied to me. I agree to conduct the study in accordance with ICH GCP guidelines, and applicable local legal and regulatory requirements.

Investigator Signature Date

Investigator Name (Print)

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PROTOCOL SYNOPSIS

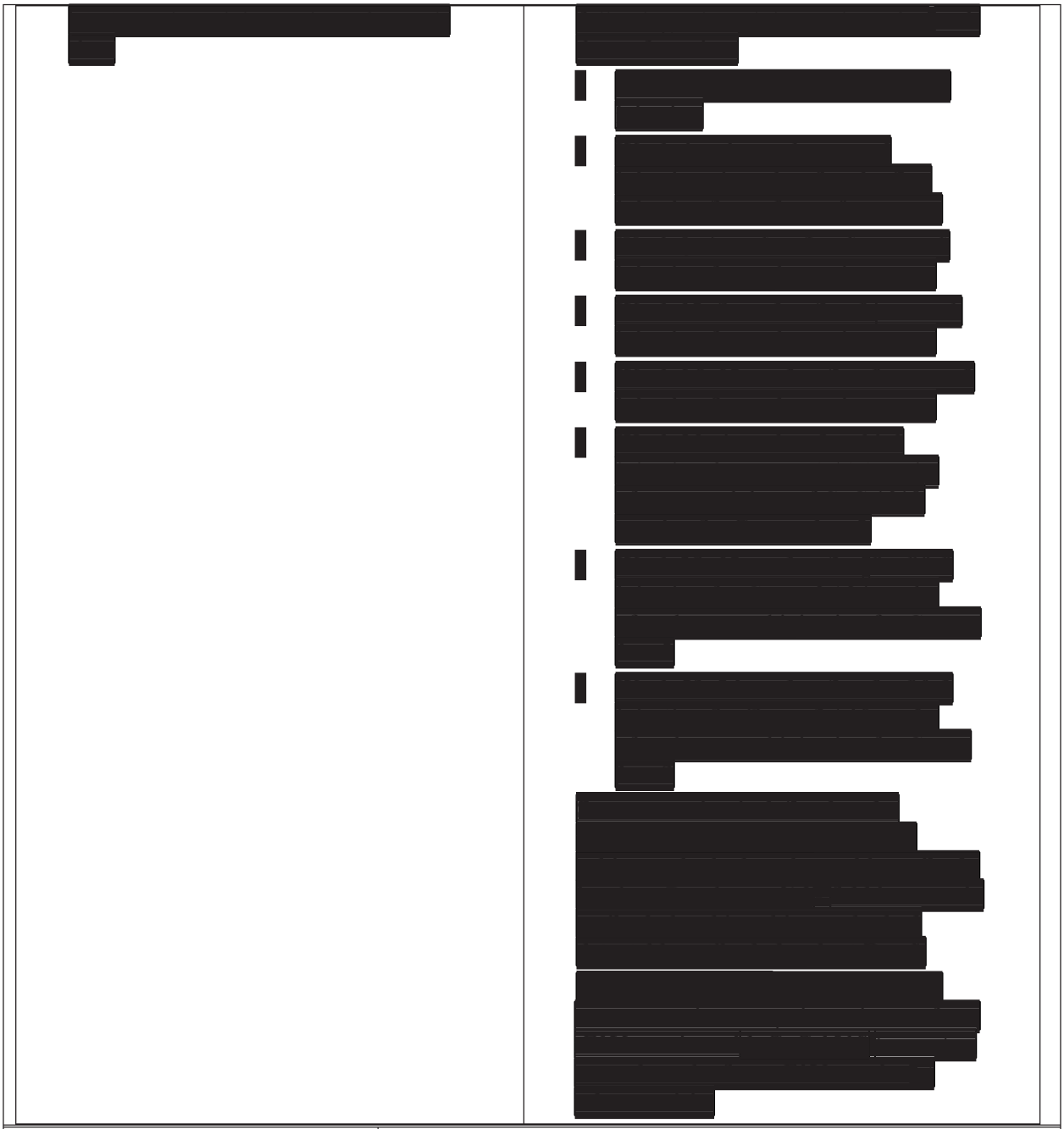
Protocol Title: Phase 2, Randomized, Active-Controlled, Observer-Blinded, Multicenter Trial of the Immunogenicity, Safety, and Tolerability of rF1V Vaccine with CpG 1018 Compared with rF1V Vaccine in Adults 18 to 55 Years of Age

Study Objectives and Endpoints:

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 [redacted] threshold that corresponds to 50% predicted vaccine efficacy after 2 doses of rF1V vaccine with CpG 1018 at Day [redacted] compared to that after 3 doses of rF1V vaccine at Day [redacted]
• To assess the serum [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 Day [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 l, 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]	
[redacted]	[redacted]
[redacted] s EI	[redacted] r r
[redacted]	[redacted]
[redacted]	[redacted]



Study Design:	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 study Days [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 unblinded 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 administration methods of rF1V vaccine with CpG 1018:

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

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

- Group 3 (N = approximately 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.

A Data Monitoring Committee (DMC) will review safety for Part 1 after the first dose:

- 72 hours after first dose in the first 6 subjects
- 14 days after first dose in the first 18 subjects

In addition, the DMC may review safety data as needed at any time during the study (as defined in the DMC charter).

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 1 month after 2 doses of rF1V vaccine in Group 3. Prior to enrolling subjects in Part 2, the Pharmacy Manual will be updated to document the method of administration of rF1V vaccine and CpG 1018 selected for Part 2.

Part 2:

Part 2 will begin after immunogenicity assessments from the [redacted] visit in Part 1 are completed. The rF1V vaccine with CpG

	1018 will be administered using the method selected from Part 1 (Group 1 or Group 2). • Group 1 (if selected) (N=70): rF1V co-administered with CpG 1018 • Group 3 (N=70): rF1V co-administered with placebo **OR** • Group 2 (if selected) (N = 70): bedside mix of rF1V and CpG 1018 • Group 3 (N=70): rF1V Subjects will be followed through Day 393 (Week 56)
Study Duration	• The total duration of individual subject participation in the Screening Treatment and Follow-up parts of this study is up to approximately 60 weeks.
Study Population:	Adults 18 to 55 years of age
Planned Number of Participants:	Part 1: N = approximately 60 Part 2: N = approximately 140
Eligibility Criteria:	**Inclusion Criteria** A subject must meet the following criteria to be eligible for enrollment (defined as receiving study treatment) in the study: 1) Adults aged 18 to 55 years 2) Healthy participants or participants with pre-existing medical conditions who are in a stable medical condition. *Pre-existing stable medical condition means a subject who: has full capacity of daily activity and no major medication modification within 3 months prior to Day 1; has not undergone surgical or minimally-invasive intervention or had any hospitalization/emergency room visit for the specific medical condition.* 3) Able to comply with the protocol schedule and procedures 4) Able and willing to provide written informed consent 5) If female of child-bearing potential and heterosexually active, has practiced adequate contraception for 28 days prior to vaccination and has negative pregnancy tests just prior to vaccination and has agreed to continue adequate contraception until 28 days after vaccination. Adequate contraception is defined as a contraceptive method with a failure rate of < 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. Examples include the following: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal

- Progestin-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
- Intrauterine device (IUD) with or without hormonal release
- Vasectomized partner, provided he is the subject's sole partner and that he has received a medical assessment of the surgical success
- Credible self-reported history of heterosexual abstinence for at least 28 days prior to vaccine administration
- Female partner

Female subjects of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy) or postmenopausal (defined as amenorrhea for 2' l2 consecutive months prior to Screening without an alternative medical cause).

Exclusion Criteria

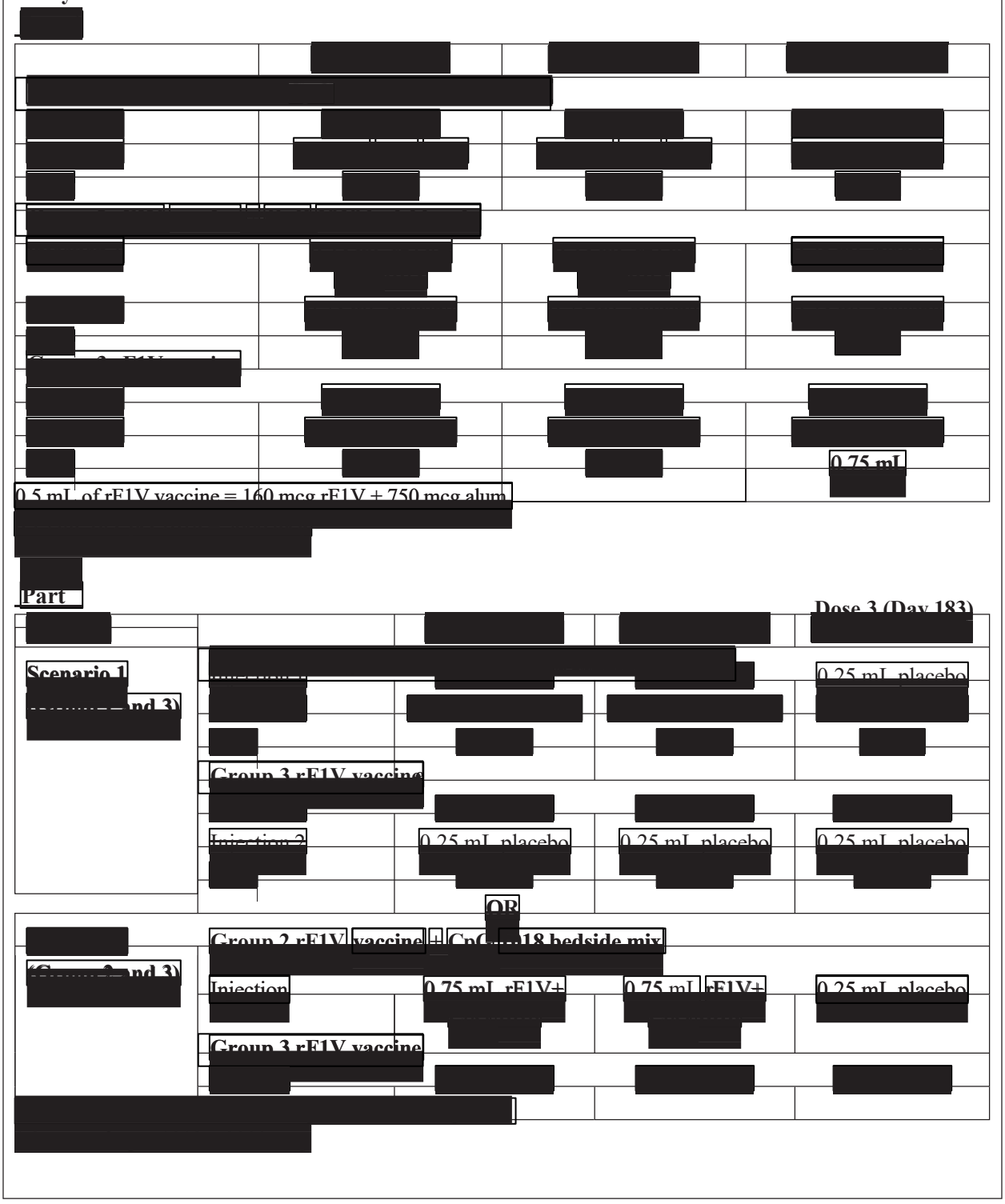
A subject with any 1 of the following criteria is not eligible for enrollment (defined as receiving study injection) in the study:

1) A history of plague disease or have previously received any plague vaccine.
2) Active tuberculosis or other systemic infectious process.
3) History of human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) infection, or positive test for antibody to HIV, HBV, or HCV
4) History of autoimmune disorder
5) History of sensitivity to any component of study vaccines
6) Body mass index 2' 30 kg/m2
7) Has received the following prior to the injection:
   - **:: 14 days:**
     - Any licensed COVID-19 vaccine or any inactivated vaccines (including vaccines containing mRNA or CpG)
   - **:: 28 days:**
     - Any live vaccine
     - Systemic corticosteroids (more than 3 consecutive days) or other immunomodulators immune suppressive medication, with the exception of inhaled steroids
     - Any other investigational medicinal agent
   - **:: 90 days:**
     - 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:** DNA plasmids or other genetic therapy intended to integrate permanently into host cells 8) If female is pregnant (known before or established at the time of screening), breastfeeding, or planning breastfeeding or a pregnancy 9) Is undergoing chemotherapy or expected to receive chemotherapy during the study period; has a diagnosis of cancer within the last 5 years other than squamous cell or basal cell carcinoma of the skin 10) History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator 11) Oral temperature >100.0°F at the time of vaccine administration. 12) History of acute myocardial infarction (AMI) or documented coronary artery disease (CAD)
Study Treatments:	**Investigational Medicinal Product:** • Recombinant F1V (rF1V) plague antigens with aluminum hydroxide • CpG 1018 • Placebo (normal saline) **Dose and Administration:** 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). <u>Part 1</u> Group 1: 0.5 mL of rF1V vaccine (160 mcg rF1V + 750 mcg alum) and 0.25 mL of CpG 1018 (3000 mcg) will be administered intramuscularly in the deltoid muscle of the non-dominant arm on <u>Days 1</u> [redacted] Group 2: 0.75 mL of the bedside mix of rF1V vaccine and CpG 1018 (0.5 mL and 0.25 mL respectively) and 0.25 mL of placebo will be administered intramuscularly in the deltoid muscle of the

	non-dominant arm on Days 1 [redacted]. Group 3: 0.5 mL of rF1V vaccine and 0.25 mL of placebo will be administered intramuscularly in the deltoid muscle of the non-dominant arm on Days [redacted]. Part 2 **Scenario 1: Group 1 is selected.** Group 1: 0.5 mL of rF1V vaccine and 0.25 mL of CpG 1018 will be administered intramuscularly in the deltoid muscle of the non-dominant arm on Days 1 [redacted]. Group 3: 0.5 mL of rF1V vaccine and 0.25 mL of placebo will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted] **Scenario 2: Group 2 is selected.** Group 2: 0.75 mL of the bedside mix of rF1V vaccine and CpG 1018 will be administered intramuscularly in the deltoid muscle of the non-dominant arm on Days 1 [redacted] Group 3: 0.5 mL of rF1V vaccine will be administered intramuscularly the deltoid muscle of the non-dominant arm on Days [redacted]

Study Vaccine Administration



Safety Assessments	All subjects will be monitored for safety through Day 393. Safety assessments include the following: • Assessment of post-injection local and systemic reaction (for 7 days post each injection) • Adverse events assessments (AEs, SAEs, AESIs, deaths) • Vital signs measurements • Physical examinations
Stopping Rules	Dosing of all subjects will be temporarily stopped for any of the following: • Two or more subjects who experience Grade 3 (severe) or higher severity solicited adverse reactions (considered by the sponsor to be possibly or probably related to treatment) lasting more than 48 hours AND considered by the DMC to be clinically significant • Two or more subjects who experience the same or similar grade 3 or higher unsolicited adverse event that is assessed as at least possibly related to the treatment • Any Suspected Unexpected Serious Adverse Reaction (SUSAR) (considered by the Sponsor to be possibly or probably related to treatment) • Any death or life-threatening SAE regardless of relationship to vaccine • Any type 1 AMI Dosing may be resumed following review of available safety data by the DMC as specified in the DMC Charter.
Immunogenicity Assessments:	Immunogenicity assessments include Serum rF1V Bridge ELISA concentration as outlined in the summary of trial events
Statistical Methods	All analyses of demographics, medical history, 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. 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. The modified intent-to-treat (mITT) population for the immunogenicity analysis 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 receive 2 doses of study vaccine and Group 3 subjects who received 3 doses of study vaccine, have no major protocol deviations (to be specified in the statistical analysis plan), and have

	immunogenicity data obtained within the study visit windows at Day 211. 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. The administration method of vaccine utilized in Part 2 of the study will be selected 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 1 month after 2 doses of rF1V vaccine in Group 3. [redacted] threshold that corresponds to 50% predicted vaccine efficacy after 2 doses of rF1V vaccine with CpG 1018 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. Predicted protection rate (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. The criterion for evaluation of the primary endpoint 1 in Part 2 is: a 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. The criterion for evaluation of the primary endpoint 2 in Part 2 is: 2-times increase of [redacted] GMC point estimate after the second dose of rF1V vaccine with CpG 1018 compared to that after rF1V vaccine. Criteria for secondary objectives are GMC and seroconversion rate point estimates from rF1V vaccine with CpG 1018 to meet or exceed results from rF1V vaccine at relevant visits Safety data will be analyzed descriptively and will be based on the Safety Population. Summary statistics will be used to describe the incidence of all post-injection reactions, AEs, AESIs, SAEs, and deaths. Tables of adverse events will include incidence, severity, seriousness, and relationship to the investigational vaccines. Data from Part 1 subjects and Part 2 subjects will be combined to evaluate the Part 2 objectives.

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
alum	Aluminum hydroxide
AMI	acute myocardial infarction
ANCA	anti-neutrophil cytoplasmic antibodies
AR	adverse reaction
BP	blood pressure
CAD	coronary artery disease
CBER	Center for Biologics Evaluation and Research
CD4+	T-helper cells
CFR	Code of Federal Regulations
COR	contracting officer
CpG	cytidine-phospho-guanosine
CpG 1018	a 22-base cytidine-phospho-guanosine phosphorothioate oligodeoxynucleotide
CRF	case report form
CRO	Contract Research Organization
CSR	clinical study report
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoD	Department of Defense
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EUA	emergency use authorization
FDA	Food and Drug Administration
GCP	good clinical practice
GMC	geometric mean concentration
GMR	geometric mean ratio
GMT	geometric mean titer
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	heart rate
IB	investigators brochure

ICF	informed consent form
ICH	International Council for Harmonisation
IM	intramuscular
IMAE	immune-mediated adverse events
IND	investigational new drug
IRB	Institutional Review Board
ITAR	International Traffic in Arms Regulations
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
mIU/mL	milli-international units per liter
NIH	National Institutes of Health
ODN	oligodeoxynucleotides
OVRR	Office of Vaccines Research and Review
PBMC	peripheral blood mononuclear cell
PIR	post-injection reactions
PP	per protocol
PS ODN	phosphorothioate oligodeoxynucleotide
rF1V	recombinant F1 capsular protein fused to V antigen
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SPR	seroprotection rate
TC	telephone call
TEAE	treatment-emergent adverse event
Th	T helper 1 cells
TLR9	Toll-like receptor 9
UNS	unscheduled
USG	United States Government
VAERS	Vaccine Adverse Event Reporting System
Y. Pestis	*Yersinia pestis*

2 INTRODUCTION AND RATIONALE

2.1 Plague (*Yersinia pestis)*

Plague is a zoonotic infection with *Yersinia pestis* that is normally transmitted from rodents to humans when humans are bitten by infected fleas. There are 3 manifestations of the disease, with flea bites usually causing the bubonic form in which a painful swelling (bubo) of the draining lymph nodes occurs (Vadyvaloo, Jarrett et al. 2007, Hinnebusch and Erickson 2008). Left untreated, the infection will cause sepsis and death in approximately half of the cases. Bubo formation is not present in the second form of disease, which leads directly to sepsis, and occurs in about a third of the cases. Bubonic and septicemic infections occasionally progress to secondary pneumonic infections. Infection with *Y. pestis* also rarely occurs through inhalation of the organism, and, after 1 to 6 days, the disease manifests in its pneumonic form, which is nearly always fatal unless the patient is treated with antibiotics within 20 hours of symptom onset (Daya and Nakamura 2005). Clinical signs include fever with cough and dyspnea, and there may be production of bloody, watery sputum. Nausea, vomiting, abdominal pain, and diarrhea may also be present. The pneumonic form spreads from person to person by respiratory droplets formed during coughing (McGovern 1997, Perry and Fetherston 1997, Inglesby, Dennis et al. 2000, Koirala 2006, Prentice and Rahalison 2007).

Historically, plague (*Y. pestis*) has resulted in three pandemics over the last 1,700 years. It is estimated to have caused 200 million deaths worldwide. *Y. pestis* is currently classified as a Category A priority pathogen by both the National Institute of Allergy and Infectious Diseases (NIAID) and the Centers for Disease Control and Prevention (CDC) (Hart, Saviolakis et al. 2012).

2.2 rF1V Vaccine Background

The proposed indication for *Y. pestis* Plague Recombinant Antigen (rF1V; F1 capsular protein fused to V antigen; *Escherichia coli*) (rF1V Plague Vaccine) is to provide pre-exposure prophylaxis to military personnel 18 to 55 years of age against pneumonic plague resulting from aerosol exposure to *Y. pestis*.

The rF1V plague vaccine candidate was initially developed at the US Army Medical Research Institute for Infectious Diseases (USAMRIID) (Hart, Saviolakis et al. 2012). It was transferred to the Joint Vaccine Acquisition Program (JVAP) (subsequently to the DynPort Vaccine Company [DVC], and most recently to the Office of the Surgeon General) in an early stage of development. In 2016, the U.S. Food and Drug Administration (FDA) granted Orphan Drug Designation to recombinant rF1V plague vaccine as a biodefense countermeasure on behalf of the U.S. Department of Defense (DoD). The vaccine is intended to be administered to individuals considered to be at high risk for exposure to aerosolized *Y. pestis*. The target indication of this vaccine is protection of adults 18 to 55 years of age from disease caused by inhalational exposure to *Y. pestis*.

The rF1V vaccine candidate for plague comprises the F1 capsular protein and the V virulence protein of *Y. pestis* Colorado 92 (CO92) fused into a single protein, which is produced in *E. coli* and formulated with aluminum hydroxide, Alhydrogel® 2%, (alum).

2.3 Clinical Experience with rF1V Vaccine

The rF1V vaccine was evaluated in one Phase 1 (rF1V-01), Phase 2a (rF1V-02a), and 1 phase 2b (rF1V-02b) clinical trial. In these clinical trials, assessments of vaccine safety and immunogenicity were the major objectives. The immune response to the vaccine was evaluated by measurement of the concentration of antibodies to rF1, rV, and rF1V by the [redacted] at predetermined intervals during the study and calculation of the seroconversion rate. Blood was also collected for passive transfer studies for evaluation of efficacy in animals. The safety population included all volunteers who received at least 1 dose of the rF1V vaccine and for whom any safety information was recorded. Reactogenicity, tolerability and safety were monitored in all vaccinated volunteers at multiple time points after vaccination using physical examination, clinical laboratory tests, and pre-specified or solicited adverse events (AEs) collected via volunteer diaries to enhance reporting of AEs by the Investigators.

2.3.1 Effectiveness Data with rF1V Vaccine – Bridge Strategy

The efficacy of the rF1V vaccine as a prophylactic for pneumonic plague, resulting from inhalational exposure, cannot be determined directly in humans and, therefore, was evaluated by the Dynport Vaccine Company (DVC) for the DoD in accordance with the Animal Rule. Use of the Animal Rule requires that the pathophysiology of disease and the mechanism by which the vaccine ameliorates disease is well understood in animals. The animal models that DVC selected to evaluate vaccine efficacy were the Swiss Webster mouse and the cynomolgus macaque (CM). Aerosol model development studies have been performed in both animal species and have demonstrated sufficient similarity to the pathology of disease in humans to serve as useful animal models for pneumonic plague. DVC evaluated the rF1V vaccine in these animal models for the purpose of licensure using the Animal Rule. The agreed bridging strategy for rF1V vaccine was based on modeling the animal survival status (endpoint of interest) as a function of anti-rF1V antibody concentration measured by the rF1V [redacted] (the correlate of protection).

2.3.2 rF1V Mechanism of Action

Seeking licensure for a plague vaccine provides unique challenges in that the precise mechanism of protection against exposure to *Y. pestis* is unknown. Both cell-mediated immunity and humoral immunity are relevant in providing protection against plague. The agreed bridging strategy for rF1V vaccine is supported by data that demonstrate anti-rF1V antibody concentration correlate with rF1V vaccine efficacy in animal models (establishing the relationship between rF1V vaccine dose, anti-rF1V antibody concentration, and survival in the Swiss Webster mouse model and cynomolgus macaque following lethal aerosol challenge with *Y. pestis* CO92).

Additionally, DVC demonstrated the direct functional relationship between anti-rF1V antibody concentration and survival through the conduct of the Protective Capacity Assay (PCA). The PCA uses purified antibodies collected from rF1V immunized animals or humans to measure the functional capacity of anti-rF1V antibodies in a mouse model following aerosol challenge with *Y. pestis*.

2.3.3 Clinical Evaluation of rF1V Plague Vaccine

2.3.3.1 Phase 1 Clinical Trial, Protocol rF1V-01 (NCT00097396)

[redacted]

[redacted]

2.3.3.3 Phase 2b Clinical Trial, rF1V-02b (NCT01122784)

[redacted]

2.4 CpG 1018 Background

2.4.1 CpG 1018 Mechanism of Action

CpG 1018 is a synthetic oligonucleotide containing immunostimulatory cytidine-phospho-guanosine (CpG) sequence motifs that mimic bacterial and viral DNA. CpG 1018 exerts its actions solely through a single, well-defined pattern recognition receptor in the innate immune system, Toll-like receptor 9 (TLR9), a mechanism that is distinct from other commercial adjuvants, including oil-in-water adjuvants. CpG 1018 efficiently induces dendritic cells to develop into highly effective antigen presenting cells. These activated dendritic cells drive the induction of helper T cells (Th) that are essential for the generation of antibodies and T and B cell memory to vaccine antigens. CpG-1018 is particularly effective in stimulating development of the Th1 subset of helper T cells, the Th subset that is essential for protection against most viruses and intracellular bacteria. Therefore, the mechanism of action of the CpG 1018 adjuvant is well understood and highly specific. CpG 1018 specifically activates a key innate receptor, TLR9, and does not have demonstrable off-target activities.

2.4.2 Review of Available Clinical Data Supporting Rationale for CpG 1018 with rF1V Antigen

There are no clinical data available adding CpG 1018 to rF1V antigen. There are substantial safety and immunogenicity data available where CpG 1018 has been added to hepatitis B surface antigen (HBsAg) in preventive vaccines and a growing database of CpG 1018 combined with SARS-CoV-2 spike protein with and without alum.

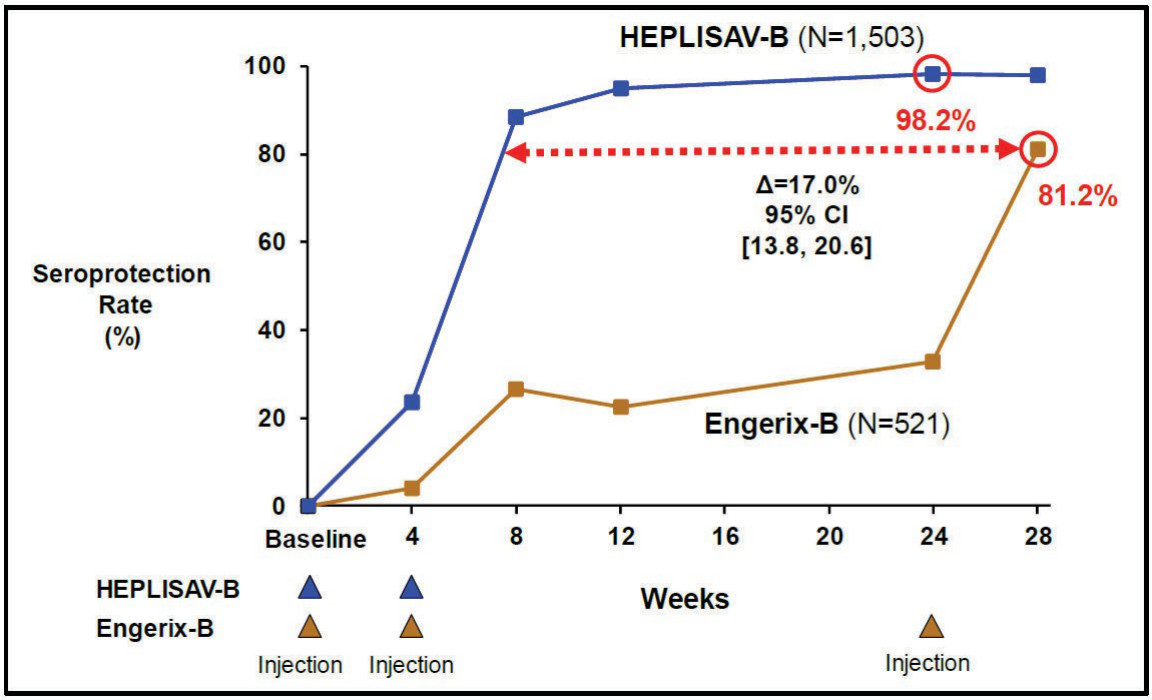
2.4.2.1 Summary of Clinical Experience in CpG 1018

2.4.2.1.1 HEPLISAV-B (CpG 1018 + HBsAg)

CpG 1018 3000 mcg with HBsAg has been evaluated in the clinical development program for HEPLISAV-B®, approved by the US FDA on 9 November 2017 (Dynavax Technologies Corporation 2020) and by the European Medicines Agency (EMA) on 18 February 2021 (Dynavax Technologies Corporation 2021). Data are available for 10,038 adult subjects between the ages of 18 and 70 years who received HEPLISAV-B in 3 phase 3 pivotal trials (HBV-10, HBV-16, and HBV-23) and 8 additional supportive trials HBV0001, HBV-02, HBV-03, HBV-04, HBV-05, HBV-08, HBV-14, and HBV-22.

In the HEPLISAV-B clinical development program of over 14,000 subjects, comparative studies of 2 doses of HEPLISAV-B (20 mcg HBsAg + 3,000 mcg CpG 1018) over 1 month (Days 1 and 29) with 3 doses of the alum adjuvanted Engerix-B® (20 mcg HBsAg + 500 mcg alum) over 6 months (Days 1, 29, and 183) showed statistically significantly higher immunogenicity in HEPLISAV-B recipients than Engerix-B recipients with a similar safety and tolerability profile. Seroprotection rates (SPR; % with antibodies to hepatitis B surface antigen [anti-HBs] 2' 10 mIU/mL) of more than 90% were produced in all populations studied and were statistically significantly higher than those induced by Engerix-B (Figure 2-2).

Figure 2-2: Example of Typical Seroprotection Rates by Visit in the Pivotal Trials (Trial HBV-10 Per Protocol Population; 18 to 55 year old adults)



(Halperin, Ward et al. 2012)
PP = Per-protocol; SPR = seroprotection rate.
Note: The median time to seroprotection of the 2-dose HEPLISAV-B schedule occurred 5 months earlier than the 3-dose Engerix-B schedule, denoted by the red arrows. Similar time courses of seroprotection were observed in HBV-16 (Heyward, Kyle et al. 2013) and HBV-23 (Jackson, Lentino et al. 2018).

In the Dynavax study HBV-10 of adults 18 to 55 years of age, the SPR at four weeks after the second dose of HEPLISAV-B, at week 8, was statistically significantly higher than the SPR in the Engerix-B group at week 8 (88.4% vs 26.7%, $p < 0.0001$). It was also significantly higher than the peak SPR following three doses of Engerix-B at week 28 (81.3%, $p < 0.001$). At week 8, the geometric mean concentration (GMC) of anti-HBs antibodies was 83.1 mIU/mL in the HEPLISAV-B group and 6.5 mIU/mL in the Engerix-B group ($p < 0.0001$). The peak GMC in the HEPLISAV-B group (341.6 mIU/mL) was similar to the peak GMC in the Engerix-B group (352.1 mIU/mL).

In summary, the CpG 1018 adjuvanted HBV vaccine, HEPLISAV-B, with a 2-dose regimen administered within 1 month induced a peak SPR, GMC, as well as duration of response greater than or similar to what was seen after 3 doses of Engerix administered over 6 months. The improved dosing schedule achieved by adjuvating HBsAg with CpG 1018 is comparable to the goal identified by the Military in this prototype project, namely accelerating the onset of protection and a non-inferior or superior immunological response to rF1V antigen in a dramatically shortened vaccination schedule.

Safety data are available for 9365 adult participants who received CpG 1018 in the three phase 3 HEPLISAV-B pivotal trials (HBV-23, HBV-16, and HBV-10) and 31,000 HEPLISAV-B recipients in a post-marketing study. In addition, over 900,000 doses of HEPLISAV-B have been distributed in the US since 2017 with benign spontaneous safety reports both to the Vaccine Adverse Events Reporting System (VAERS) and Dynavax.

HEPLISAV-B induces a similar frequency of local post-injection reactions (PIRs) and a lower frequency of systemic PIRs (including fever) compared to Engerix-B. Overall, 55.1% of subjects in the HEPLISAV-B arm experienced any PIR compared to 57.1% of subjects in the Engerix-B arm. Systemic PIRs occurred in 32.3% of the HEPLISAV-B group and 37.4% of the Engerix-B group, and local PIRs occurred in 42.8% of the HEPLISAV-B group and 41.1% of the Engerix-B group. Adverse events, serious adverse events, immune-mediated adverse events of special interest, and deaths were balanced between the HEPLISAV-B and Engerix-B groups. Changes in autoantibodies including ANA, anti-dsDNA, and ANCA were similar between vaccine groups (Hyer, McGuire et al. 2018).

2.4.2.1.2 CpG 1018 as a Biological Response Modifier in Ongoing Clinical and Preclinical Programs

Dynavax is evaluating CpG 1018 in multiple clinical development programs. In all of these studies, CpG 1018 was combined with aluminum hydroxide (ie, alum, Alhydrogel® 2%) as the adjuvant. Preclinical studies in multiple animal models, and now humans, have shown substantially greater adjuvant activity of a combination of CpG 1018 and alum than with either of the individual adjuvants. Studies in non-human primates have demonstrated the immunogenicity of two different SARS-CoV-2 spike protein antigens adjuvanted with CpG 1018 and alum (Arunachalam, Walls et al. 2021) (and unpublished data from NIH Vaccine Research Center). In the NIH study, monkeys were immunized twice with recombinant spike from the original Wuhan strain of SARS-CoV-2 and were fully protected when challenged 8 months later with the SARS-CoV-2 beta variant, demonstrating the durability and breadth of the protective antibody response. Importantly, results from human studies with multiple COVID-19 vaccine antigens utilizing CpG-1018 and alum confirm the ability of this adjuvant formulation to stimulate high levels of IgG, neutralizing antibodies, and T cell responses with a 2-dose regimen with no safety concerns (Hsieh, Liu et al. 2021, Richmond, Hatchuel et al. 2021) (Valneva and BiologicalE unpublished data).

Importantly, in two of the above studies, same day mixing of CpG-1018 with antigen and alum (Alhydrogel 2%) was employed, and the resulting mixture given as a single injection (Richmond, Hatchuel et al. 2021) (Valneva unpublished data).

The two most advanced subunit COVID-19 vaccines provide substantial evidence of the effectiveness, tolerability, and safety of the combined CpG 1018 + alum (Alhydrogel 2%) adjuvant. The immunogenicity of MCV-COV1901, a COVID-19 vaccine using the NIH SARS-CoV-2 spike protein with 750 mcg of CpG 1018 and alum was evaluated in a phase 1, open-label dose-finding study. After the second vaccination with MCV-COV1901, the spike specific IgG titers increased with peak geometric mean titers of 7178 (low antigen dose), 7746 (middle antigen dose), and 11220 (high antigen dose) (Hsieh, Liu et al. 2021). In addition, serum neutralizing activity geometric mean values were 1.8 to 3.9 times higher than those of a panel of control human convalescent sera. A phase 2 study of over 3800 participants > 19 years of age, randomized 6:1, has recently reported a geometric mean neutralization titer of 662, a GMT ratio of 163, and a seroconversion rate of 99.8% (Hsieh, Liu et al. 2021). These results meet the criteria established by the Taiwan FDA for Emergency Use Authorization. The vaccine was well tolerated with no severe adverse reactions. Injection site pain (71.2%), most of mild severity, was the most frequent post-injection reaction. The most frequent systemic post-injection reactions were fatigue (MCV-COV1901: 36%; placebo: 29.7%), myalgia (MCV-COV1901: 27.6%; placebo: 16.6%), and headache (MCV-COV1901: 22.2%; placebo: 20%). Fever was uncommon (MCV-COV1901: 0.7%; placebo: 0.4%) (Hsieh, Liu et al. 2021)

The safety and immunogenicity of the second COVID-19 vaccine, SCB-2019, were evaluated in a phase 1, randomized, double-blind, placebo-controlled dose-finding study in healthy adults (Richmond, Hatchuel et al. 2021). SCB-2019 is a protein subunit vaccine candidate containing a stabilized trimeric form of the SARS-CoV-2 spike protein (S-Trimer) combined with 1500 mcg of CpG 1018 and 750 mcg of alum. SCB-2019 with no adjuvant elicited minimal immune responses, but adjuvanted SCB-2019 induced high titers and seroconversion rates of binding and neutralizing antibodies. IgG responses were observed at all dose levels after the first dose, but titers were greatly increased after the second dose, with GMTs of 478–2440 on Day 36. High GMTs were maintained to Day 50, when seroconversion rates were 87.5–93.8%. CpG 1018 + alum titers were 2.1-fold higher than those recorded in a panel of convalescent sera from patients with COVID-19. SCB-2019 elicited Th-1-biased CD4+ T-cell responses.

In a follow up analysis (Richmond, Hatchuel et al. 2021), immunoglobulin G (IgG) antibodies were measured against SCB-2019, angiotensin-converting enzyme 2 (ACE2) competitive binding antibodies, and neutralizing antibodies against wild-type SARS-CoV-2 (Wuhan-Hu-1) at Days 101 and 184, and neutralizing antibodies against 3 VoCs, Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1), in Day 36 sera. Titers waned from their peak at Days 36–50, but SCB-2019 IgG antibodies, ACE2 competitive binding antibodies, and neutralizing antibodies against wild-type SARS-CoV-2 persisted at 25%–35% of their observed peak levels at Day 184. Day 36 sera also demonstrated dose-dependent increases in neutralizing titers against the 3 VoCs.

The vaccine was well tolerated with no severe adverse reactions. Injection site pain (62.5), most of mild severity, was the most frequent post-injection reaction. The only systemic post-injection reactions were headache (SCB-2019: 25.0%; placebo: 14.3) and fatigue (SCB-2019: 12.5%; placebo: 0).

Based on a model by Khoury and colleagues (Khoury, Cromer et al. 2021), both vaccines, with a ratio of neutralizing antibodies to antibodies in human convalescent sera greater than 2, are likely to have an efficacy against COVID-19 greater than 85% to 90%.

2.5 Study Rationale and Doses to Be Evaluated

Dynavax will conduct an adaptive clinical trial to determine if CpG 1018, the adjuvant used in HEPLISAV-B, can be utilized as a Biological Response Modifier (BRM) to improve the operational utility of the current investigational rF1V vaccine for the Military without re-formulation of the adjuvant. Dynavax will evaluate both coadministration (rF1V and CpG 1018 administered in two concurrent injections in the same location), and a bedside mix (rF1V and CpG 1018 combined in a single syringe prior to vaccination) compared to rF1V alone to determine the method of administration that provides an acceptable immune response conducive to field deployment. A two-dose schedule at Day [redacted] and Day [redacted] will be tested which would enhance military rapid-response capabilities afforded by the investigational rF1V vaccine. Dynavax has designed the trial to be powered to support the current rF1V pre-Emergency Use Authorization. Completion of the proposed prototype project will support the development of next generation rF1V vaccine(s) with an enhanced operational utility for the military and for the prevention and/or curtailment of a pneumonic plague outbreak.

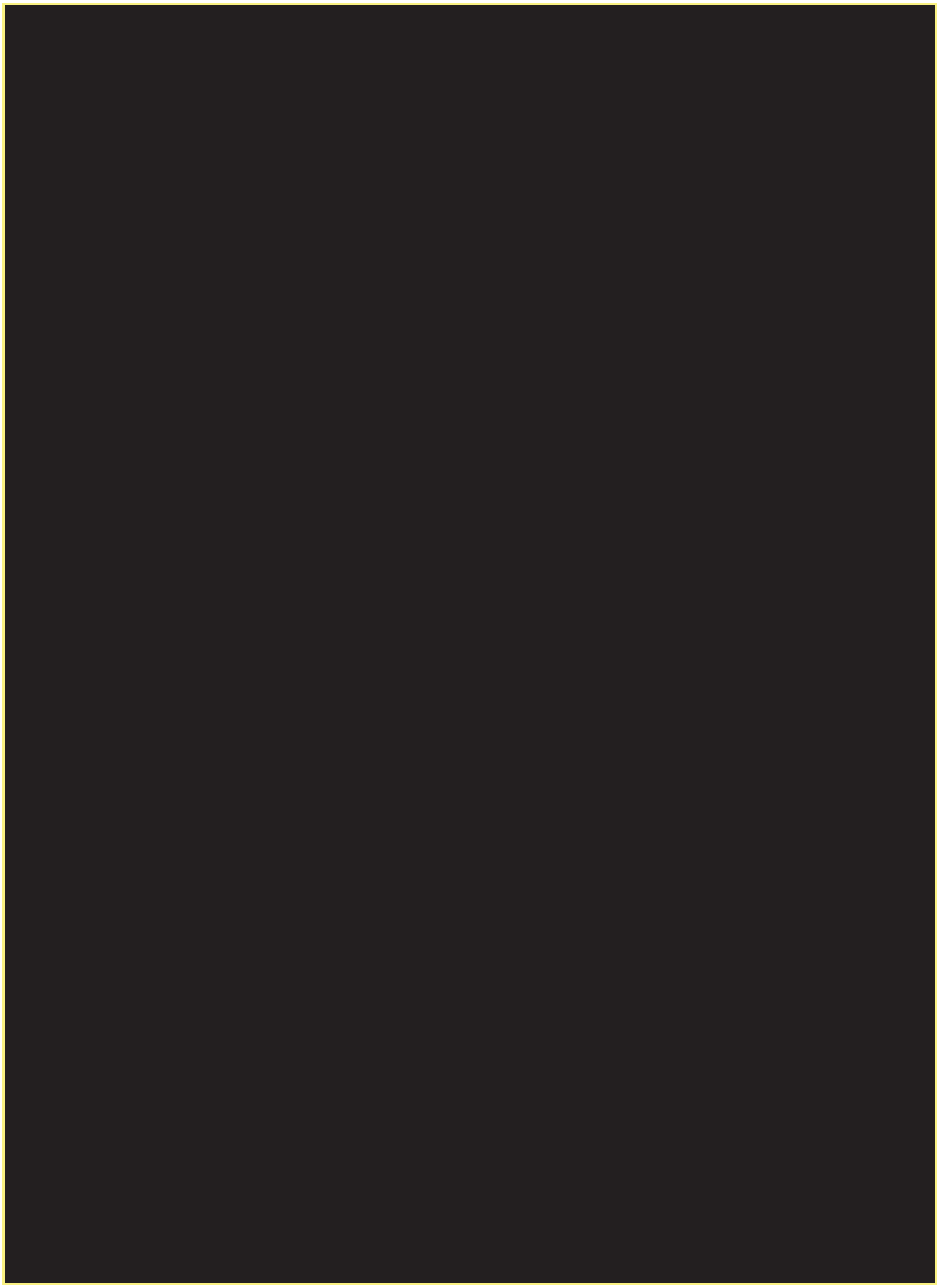
3 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are:

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 [redacted] threshold that corresponds to 50% predicted vaccine efficacy after 2 doses of rF1V vaccine with CpG 1018 at Day [redacted] compared to that after 3 doses of rF1V vaccine at Day [redacted]

• To assess the serum [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 Day [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]

	• [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. **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]	



		[redacted]

4 INVESTIGATIONAL PLAN

4.1 Study Design

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 study Days [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 [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 Days [redacted]

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

- Group 3 (N=20): rF1V 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.

A Data Monitoring Committee (DMC) will review safety for Part 1 after the first dose:

- 72 hours after first dose in the first 6 subjects
- 14 days after first dose in the first 18 subjects

In addition, the DMC may review safety data as needed at any time during the study (as defined in the DMC charter).

The administration method of vaccine utilized in Part 2 of the study will be selected by Dynavax in consultation with the DoD after Day [redacted] 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 the 4 weeks after 2 doses of rF1V vaccine in Group 3. Prior to enrolling subjects in Part 2, the Pharmacy Manual will be updated to document the method of administration of rF1V vaccine and CpG 1018 selected for Part 2.

- Part 2: Part 2 will begin after immunogenicity assessments from the Day [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)

4.2 Study Duration

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.

4.3 Randomization and Blinding

This is an observer-blinded clinical study. Both the study subjects and the study personnel involved in safety assessment (observers) will be blinded to treatment assignments. Designated unblinded study-site personnel will be responsible for preparing and administering the study injection.

In Part 1, subjects will be randomized 1:1:1 to Group 1, 2, or 3. In Part 2, subjects will be randomized 1:1 to 1 of 2 groups (ie, either Group 1 and 3 or Group 2 and 3) as determined from Part 1. Randomization will be stratified by site.

4.4 Appropriateness of Measurements

The measures of both immunogenicity and safety in the study are routine clinical and laboratory procedures. Antibody response to rF1V must be above the assay defined cut-offs to be considered seropositive.

The secondary and exploratory evaluation of immunologic responses is based on recently developed and validated assays appropriate for use on serum that will provide deeper understanding of the quality of the immune response induced by rF1V and CpG 1018.

5 SELECTION OF SUBJECTS

5.1 Inclusion Criteria

A subject must meet all the following criteria to be eligible for enrollment (defined as receiving any study vaccine) in the study:

1) Adults aged 18 to 55 years
2) Healthy subjects or subjects with pre-existing medical conditions who are in a stable medical condition.

   Pre-existing stable medical condition means a subject who within 3 months prior to Day 1: has full capacity of daily activity and no major medication modification; has not undergone surgical or minimally-invasive intervention or had any hospitalization/emergency room visit for the specific medical condition.
3) Able to comply with the protocol schedule and procedures.
4) Able and willing to provide written informed consent
5) If female of child-bearing potential and heterosexually active, has practiced adequate contraception for 28 days prior to vaccination and has negative pregnancy tests just prior to vaccination and has agreed to continue adequate contraception until 28 days after last study injection. Adequate contraception is defined as a contraceptive method with a failure rate of < 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. Examples include the following:
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
   - Progestin-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
   - Intrauterine device (IUD) with or without hormonal release
   - Vasectomized partner, provided he is the subject's sole partner and that he has received a medical assessment of the surgical success
   - Credible self-reported history of heterosexual abstinence for at least 28 days prior to vaccine administration
   - Female partner

5.2 Exclusion Criteria

A subject with any 1 of the following criteria is not eligible for enrollment (defined as receiving any study vaccine) in the study:

1) A history of plague disease or have previously received any plague vaccine.
2) Active tuberculosis or other systemic infectious process.
3) History of human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) infection, or positive test for antibody to HIV, HBV, or HCV
4) History of autoimmune disorder (Appendix 3)
5) History of sensitivity to any component of study vaccines
6) Body mass index 2' 30 kg/m^2
7) Has received the following prior to the injection:
   - **:: 14 days:**
     - Any licensed COVID-19 vaccine or any inactivated vaccines (including vaccines containing mRNA or CpG)
   - **:: 28 days:**
     - Any live vaccine
     - 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
   - **:: 90 days:**
     - Antisense oligonucleotides
     - Granulocyte or granulocyte-macrophage colony-stimulating factor
     - Immunoglobulins or any blood products
     - Drugs/investigational agents with very long half-lives (defined as 2' 60 days)
   - **At any time:** DNA plasmids or other genetic therapy intended to integrate permanently into host cells
8) If female is pregnant (known before or established at the time of screening), breastfeeding, or planning a pregnancy
9) Is undergoing chemotherapy or expected to receive chemotherapy during the study period; has a diagnosis of cancer within the last 5 years other than squamous cell or basal cell carcinoma of the skin

10) History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

11) Oral temperature >100.0°F at the time of vaccine administration.

12) History of acute myocardial infarction (AMI) or documented coronary artery disease (CAD)

5.3 Criteria for Discontinuation of Individual Subjects From Receiving Additional Study Injections

The investigator will discontinue dosing of an individual subject and notify the sponsor within 24 hours if the subject experiences an AE including any of the following:

- Grade 4 post-injection reaction (PIR) within 7 days after any study injection
- Clinically significant Grade 3 or higher systemic reaction (eg, angioedema, generalized urticaria) within 7 days after any study injection
- Grade 3 or 4 hypotension within 24 hours of any study injection
- Grade 3 or 4 respiratory reaction or symptoms occurring within 24 hours of any study injection
- Any life-threatening AE, regardless of relationship to study drug
- Any AMI
- Any confirmed immune-mediated AE
- Violation of protocol eligibility criteria
- Subject received prohibited medications
- SAE assessed as a suspected adverse reaction (SAR) or adverse reaction (AR)
- Subject becomes pregnant or begins breastfeeding

If the subject is not eligible for subsequent study injections, **the subject will not be withdrawn from the study**, but, if possible, will be followed for safety through End-of-Study (EOS) Visit.

5.4 Removal of Subjects From the Study

Subjects may choose to withdraw from the study at any time. The reason for withdrawal will be recorded on the case report form (CRF).

Subjects may also be discontinued from the study by the investigator for any of the following reasons:

- Subject does not receive a dose of study vaccine

- Noncompliance with study procedures as determined by the investigator or sponsor
- At the discretion of the investigator if it is felt to no longer be in the best interest of the subject to remain in the study
- The sponsor decides to terminate the study

The investigator or designee should discuss with the medical monitor prior to withdrawing a subject from the study before study completion.

- If a subject discontinues, the End of Study (EOS) assessments should be completed. Required procedures are listed in Section 9.7 and in the Schedule of Events (Appendix 1).
- Additional information about terminating the study may be found in Section 6.

5.5 Replacement of Subjects

Subjects randomized and not treated may be replaced at the discretion of the Dynavax medical monitor.

5.6 Study Termination

The sponsor reserves the right to terminate the study at any time. Reasons for discontinuation of the study include but are not limited to:

- Inability to enroll sufficient subjects into the study
  - Good clinical practice (GCP) compliance issues that compromise the validity of the study
  - Emerging safety or efficacy data that deem the study unethical or impractical for continuation

Procedures for withdrawal of individual subjects can be found in Section 5.3.

6 STUDY TREATMENT AND SUPPLIES

6.1 Study Treatments

6.1.1 rFIV Vaccine

rFIV vaccine is comprised of Y. pestis plague recombinant antigen (F1 capsular protein and the V virulence protein of *Y. pestis* Colorado 92 [CO92] fused into a single protein) adsorbed to Alhydrogel® (aluminum hydroxide).

The rF1V Plague Vaccine is a liquid formulation, containing no preservatives, in 3 mL, single dose USP Type 1 glass vials with a latex-free butyl stopper and aluminum flip-off seal containing 0.8 mL of the vaccine, and each dose of 0.5 mL contains 160 mcg rF1V, 750 mcg aluminum hydroxide (alum, Alhydrogel®) and phosphate buffer.

Please refer to the Investigator's Brochure and Pharmacy Manual for additional information.

6.1.2 CpG 1018

CpG 1018 adjuvant solution (12 mg/mL) is a clear to slightly opalescent, colorless to pale yellow liquid dosage form. CpG 1018 is formulated in 20 mM Tris, 100 mM NaCl pH 7.5 buffer. Each vial contains 6 mg of CpG 1018 formulated in 0.5 mL at a concentration of 12 mg/mL in a single-use 2 mL, clear glass vial with rubber stopper and flip-off aluminum seal.

Please refer to the rF1V Vaccine with CpG 1018 Investigator's Brochure for additional information.

6.1.3 Placebo

Placebo will be normal saline.

6.2 Instructions for Preparation and Administration

6.2.1 rFIV vaccine and CpG 1018 Preparation

Please refer to the Pharmacy Manual for additional information.

6.2.2 Study Vaccine Administration

Designated unblinded study-site personnel will be responsible for preparing and administering the study injection. These individuals will not be blinded to the treatment assignment in order to prepare and administer the study injections, which will be prepared at a location isolated from blinded personnel. These individuals will not be involved in assessing safety and laboratory data and will be instructed not to communicate treatment assignments to blinded study personnel.

The unblinded study personnel should ensure that a physical barrier is used to obstruct the view of the investigational product and that the subject turns their head away from the arm being injected to prevent the subject becoming aware of their treatment assignment.

6.2.2.1 Part 1

Group 1: 0.5 mL of rF1V vaccine and 0.25 mL of CpG 1018 will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted].

Group 2: 0.75 mL of the bedside mix of rF1V vaccine and CpG 1018 and 0.25 mL of placebo will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted].

Group 3: 0.5 mL of rF1V vaccine and 0.25 mL of placebo will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted].

6.2.2.2 Part 2

Scenario 1: Group 1 is selected.

Group 1: 0.5 mL of rF1V vaccine and 0.25 mL of CpG 1018 will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted]

Group 3: 0.5 mL of rF1V vaccine and 0.25 mL of placebo will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted]

Scenario 2: Group 2 is selected.

Group 2: 0.75 mL of the bedside mix of rF1V vaccine and CpG 1018 will be administered intramuscularly in the deltoid muscle of the non-dominant arm on Days [redacted] and 0.25 mL placebo will be administered on Day [redacted]

Group 3: 0.5 mL of rF1V vaccine will be administered intramuscularly in the same or nearby location of the deltoid muscle of the non-dominant arm on Days [redacted]

Study treatments are presented in Table 7-1.

6.3 Labeling

rF1V vaccine and CpG 1018 adjuvant solution will be provided for the study and labeled for clinical study use.

At a minimum, both rF1V vaccine and CpG 1018 adjuvant solution will be labeled with the following information: product name, product lot number, contents, volume, concentration, sponsor name, and a statement indicating that the drug is for investigational use only.

6.4 Storage and Handling Instructions

The clinical supplies storage area at the site must be monitored closely by the designated site staff for temperature consistency and documentation of temperature monitoring must be maintained. Temperature excursions outside of the recommended storage range may impact product quality and must be reported to Dynavax or its designee per the detailed instructions in the Pharmacy Manual.

6.4.1 rF1V and CpG 1018

Both rF1V vaccine and CpG 1018 must be kept under refrigeration (2°C to 8°C). After preparation of drug product, it must be used within 6 hours.

Do not freeze. If product is frozen, do not use. A Pharmacy Manual will be provided with specific instructions for management of temperature excursions.

6.4.2 Bedside mix of rF1V vaccine and CpG 1018

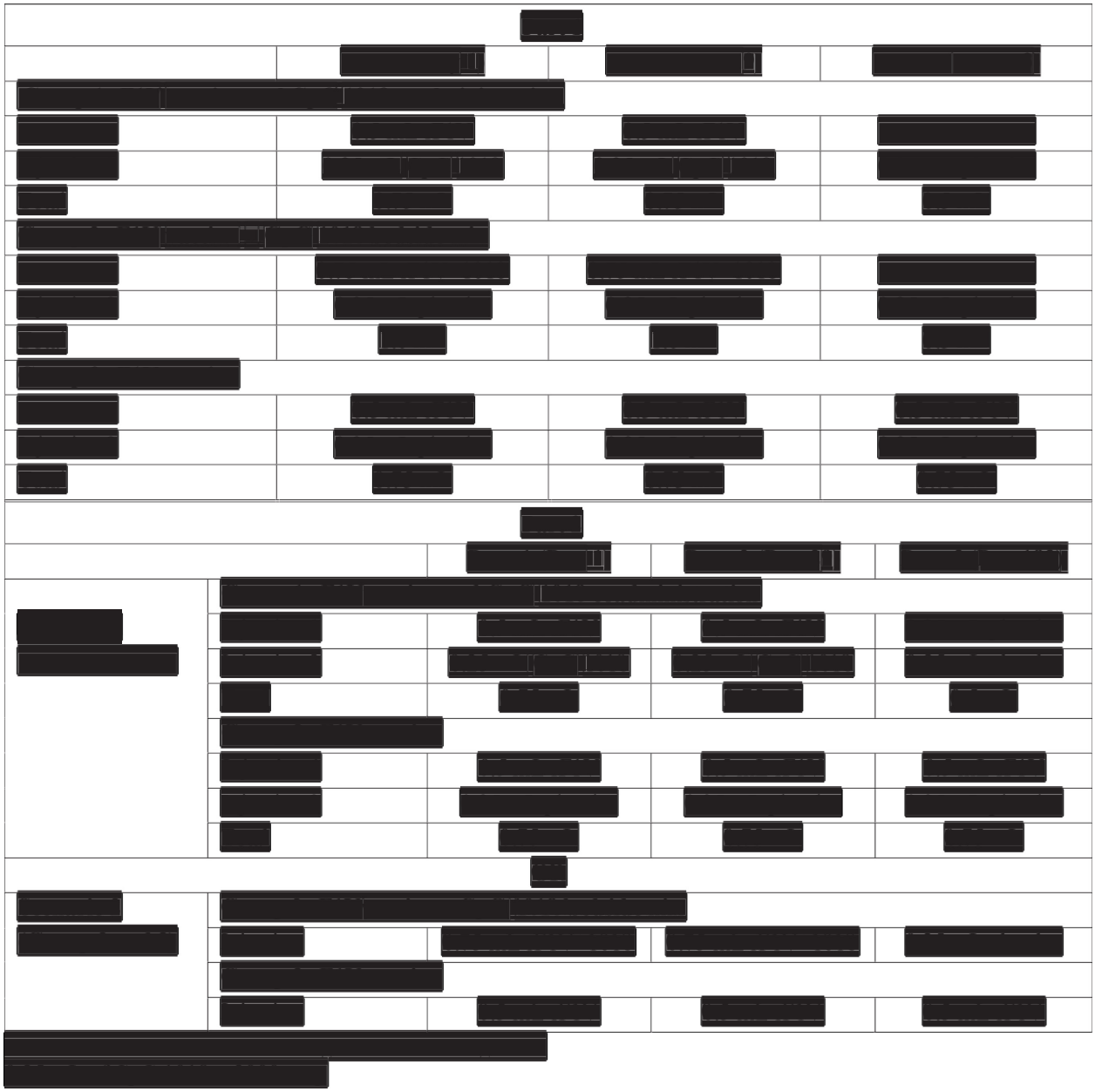
Please refer to the Pharmacy Manual for additional information.

7 TREATMENT OF SUBJECTS

7.1 Study Treatments

Study treatments are presented in Table 7-1. For each dose, injections are to be administered in the order specified in the table.

Table 7-1: Study Treatments



7.2 Dosage and Dosage Regimen

Subjects will receive their assigned vaccine on Day

7.3 Treatment Compliance

All study injections will be administered by the designated unblinded study personnel only.

7.4 Control and Accountability of Investigational Medicinal Product

All investigational medicinal product (IMP) must be received by a trained designated person at the study site, handled and stored safely and properly, and kept in a secured location with limited access.

The investigator (or responsible designee) must maintain current and accurate records of the receipt (documentation from shipments of study treatments received), administration (by subject and overall accounting) and return of study treatments to a Dynavax-specified facility for destruction (or destroyed by procedures approved by Dynavax). All study treatments must be stored in a location with access restricted to authorized personnel only.

A study monitor will be responsible for monitoring the drug accountability at the site. The study monitor should be contacted with any questions concerning administration of study treatments.

Records of study treatment accountability, storage, and handling must be made available to the study monitor for the purposes of study treatments accountability. Any discrepancy and/or deficiency must be recorded with an explanation.

Unless superseded by Standard Operating Procedures (SOPs), the investigator must retain all used vials, expired vials, damaged vials, and unused vials of study vaccine until accountability has been confirmed by the study monitor. Any exceptions to this policy must be specifically granted by Dynavax or its designee.

At the end of the study, or upon request by Dynavax, all used, partially used, and unused study treatments must be destroyed by procedures approved by Dynavax or returned to a Dynavax-specified facility for adequate disposition.

Refer to the Pharmacy Manual for detailed instructions on handling, control, and accountability of study vaccine.

Study vaccine may not be used for any purpose other than that described in this protocol.

7.5 Concomitant Medications

7.5.1 Prohibited Treatments or Therapies

The following non-study medications are prohibited:

- **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 Week 26 (Day 183):
    - 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 Week 26 (Day 183):
    - 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 Week 26 (Day 183):
    - DNA plasmids or other genetic therapy intended to integrate permanently into host cells

If a subject requires treatment that is prohibited, **the subject will not be withdrawn from the study** but will be followed for safety through Week 56.

7.5.2 Permitted Therapy

Use of any permitted medications, including over-the-counter medications or vaccine(s) during the 28 days prior to the first study vaccine injection through Week 56 or Early Discontinuation/EOS Visit, should be solicited from each subject and recorded in source documents. Use of vitamins and dietary supplements will not be collected. Medications started prior to dosing, and any medication used within the 28 days prior to dosing will be recorded.

All collected concomitant medications will be recorded in the CRF.

8 MANAGEMENT OF SUBJECT SAFETY

8.1 Data Monitoring Committee

The Sponsor will establish a DMC for this study. The DMC members and procedures will be described in the DMC charter.

8.2 Potential Reasons for Stopping the Study

Dosing of all subjects will be temporarily stopped for any of the following:

- Two or more subjects with Grade 3 (severe) or higher severity solicited adverse reactions (considered by the sponsor to be possibly or probably related to treatment) lasting more than 48 hours AND considered by the DMC to be clinically significant
- Two or more subjects who experience the same or similar grade 3 or higher unsolicited adverse event that is assessed as at least possibly related to the treatment
- Any Suspected Unexpected Serious Adverse Reaction (SUSAR) (considered by the Sponsor to be possibly or probably related to treatment)
- Any death or life-threatening SAE regardless of relationship to vaccine
- Any type 1 acute myocardial infarction

Dosing may be resumed following review of available safety data by the DMC, as specified in the DMC Charter.

8.3 Injection Site Reactions

Injection-site reactions are expected to spontaneously subside. Local pruritus and pain can be treated with oral medications. If significant symptoms of pain and induration persist for more than 12 hours, an ice pack may be applied locally for 30 minutes every 2 hours, as needed. Use of an ice pack prior to 12 hours after the onset of symptoms is discouraged, as it may interfere with the action of the study vaccine. Do not inject into a site if local pain, tenderness, swelling, or pruritus persist from a previous injection or other cause.

8.4 Observation Period After Study Vaccine Injection

Subjects will be observed for safety for a minimum of 30 minutes after each study vaccine injection. See Section 10.0 for reporting of adverse events.

8.5 Other Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. The investigator should ensure that adequate medical care is provided to a subject for any adverse events (AEs) related to the study. For each disorder, attempts should be made to rule out other causes, which might require additional supportive care. The investigator should

inform the study medical monitor when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

An unscheduled visit (UNS) should be performed if there are suspected subject safety concerns. All supportive therapies will be recorded in the subject's electronic case report form (eCRF).

Subjects who are discontinued from the study will complete the Early Discontinuation/EOS Visit, if possible, not earlier than 28 days following their vaccine administration.

9 STUDY PROCEDURES

9.1 Informed Consent, Screening, and Eligibility

9.1.1 Informed Consent

The investigator or designee must review the informed consent form (ICF) with each prospective subject to be certain that the prospective subject understands the procedures and risks of the study. Prospective subjects who wish to participate in the study must provide written informed consent by signing the ICF before undergoing any screening procedures.

The information from the consent form should be translated and communicated to the subject in language understandable to the subject and/or legal representative.

A copy of the signed and dated consent form should be offered to the subject or subject's legally acceptable representative before participation in the study. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The investigator or designee will maintain a log of all subjects who sign the ICF. At a minimum, the log will include a subject identifier, the dates of informed consent and screening procedures, the outcome of the screening, and, if a screen failure, the reason the subject did not enroll in the study. Other items that will be collected on consented participants are age, sex, ethnicity and race. These will be captured in the study database.

Additional requirements for informed consent are presented in Section 13.2.

9.1.2 Screening and Eligibility

After written consent is obtained, screening procedures must be carried out per the Schedule of Events (Appendix 1). Subjects who fail screening may not be rescreened. Subjects may have the screening window extended an additional 7-calendar days if they have equivocal laboratory results or if they cannot be enrolled during the screening window. The screening window may only be extended one time and must have prior approval by the sponsor's medical monitor. A subject must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study (Section 5.0). Documentation to support a subject's eligibility must be in the study records.

9.1.3 Demographics and Medical and Medication History

Demographic and baseline characteristics of sex, race, ethnicity, age, weight, and height of the subject will be collected.

Medical history includes clinically significant diseases and surgeries. Concomitant medications (Section 7.5) used by the subject within 28 days prior to Day 1 of the study will be recorded.

9.2 Study Visits

Procedures should be performed as close to the scheduled time as possible. A detailed outline of all scheduled study procedures is provided in the Schedule of Events (Appendix 1).

The exact time at which a procedure is performed should be recorded in the subject's study records or appropriate worksheet (if applicable).

Blood collection must be performed prior to administration of the study vaccine on each vaccine administration day.

An Unscheduled (UNS) Visit (Section 9.5) should be performed if there are suspected subject safety concerns. All supportive therapies will be recorded in the subject's CRF.

All subjects should be followed for at least 28 days after the last study vaccine injection (Section 9.6).

9.3 Immunogenicity Assessments

All immunogenicity assessments will be performed in a blinded manner in participating laboratories.

9.3.1 Antibodies to rF1V

Serum samples will be obtained to measure antibodies against rF1V. On vaccine days, samples will be collected prior to administration of study vaccine. Standardized [redacted] will be used to determine serum concentrations of antibodies to rF1V.

9.4 Safety Assessments

The measures of safety in the study are routine clinical and laboratory procedures. Safety will be assessed by the reporting and analysis of post-injection reactions (PIRs), AEs, SAEs, AESIs, and deaths (Section 10.0). The safety assessments are described below. The timing for Safety Assessments is provided in the Schedule of Events (Appendix 1).

9.4.1 Vital Signs

Vital signs will include oral temperature and measurements of heart rate, respiratory rate, systolic and diastolic blood pressure. Vital signs taken at the Day 1, Day 29, and Day 183 visits will be measured prior to study vaccine administration.

Vital signs will be recorded as indicated in the Schedule of Events (Appendix 1).

9.4.2 Physical Examinations

The investigator or qualified designee will conduct physical examinations. A complete physical examination is conducted at Screening. A symptom-directed physical exam at all other timepoints as outlined in Appendix 1.

9.4.3 Laboratory Assessments

Laboratory assessments are listed below and will be performed according to the Schedule of Events (Appendix 1). Sample collections will be prior to administration of the study vaccine on injection days.

- HIV, HBV, HCV testing at Screening Visit
- Pregnancy testing: For female of childbearing potential (ie, onset of menarche), a serum pregnancy test will be performed at screening and must be negative for the subject to participate. Additionally, a urine pregnancy test will be performed within 24 hours prior to administration of each study vaccine and must be negative for the subject to receive study injection.
- Chemistry Panel: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), bilirubin, alkaline phosphatase
- Hematology: red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, and platelet count
- Reserve serum aliquot specimens will be collected and stored frozen at a central location for possible future testing

Additional details for collection and processing of laboratory samples are provided in the Laboratory Manual.

9.4.4 Post-Injection Reaction Assessments

Assessments of PIRs (Section 10.2) will be collected for a minimum of 30 minutes following each study injection at the clinical site.

On Day [redacted] subjects will be asked to complete an e-diary (or equivalent) to record any solicited local (pain, redness, pruritus [itchiness], and swelling at the injection site) and solicited systemic signs and symptoms (fatigue, temperature, chills, malaise, myalgia, gastrointestinal symptoms, and headache) during the 7-day follow-up period after vaccination. The severity of the post-injection reactions will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 2).

PIRs persisting beyond 7 days after each study injection are considered AEs and should be recorded and reported as AEs. These will be included in the electronic data capture (EDC) AE dataset.

PIRs inadequately recorded by the subject in the e-diary and occurring during the diary period from Day 1 through Day 7 following each study injection can be reconstructed by the investigator in the AE CRF page. These will be included in the EDC AE dataset.

Refer to the eCRF completion guidelines for additional details.

9.4.5 Adverse Events

All AEs, as defined in Section 10.0, will be evaluated and reported from immediately after the study vaccine injection on Day 1 through EOS (Week 56 or Early Discontinuation) Visit. See the Schedule of Events (Appendix 1) for the AEs collection schedule.

9.4.5.1 Serious Adverse Events

All SAEs, as defined in Section 10.7.1, whether assessed as related or not related to study vaccine injection, will be evaluated from the time the consent is signed through completion of the subject's participation in the study (EOS Visit). Any SAE must be reported to Dynavax or its designee within 24 hours of knowledge of the event.

If the SAE is assessed as possibly or probably related to study treatment, it must be followed until it is considered stable or resolved, including beyond the EOS Visit.

Any SAE assessed as not related to study treatment will be followed as clinically indicated until its resolution or, if non-resolving, until it is considered chronic or stable, or until study completion (EOS Visit).

9.4.5.1.1 Type 1 Acute Myocardial Infarction (AMI)

SAEs of myocardial infarction will be further classified as Type 1 AMI if they meet the following criteria (Thygesen, Alpert et al. 2018):

- Detection of a rise and/or fall of cardiac troponin (cTn) values with at least 1 value above the 99th percentile upper reference limit and at least 1 of the following:
  - Symptoms of acute myocardial ischemia
  - New ischemic ECG changes
  - Development of pathological Q waves
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
  - Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy

9.4.6 Concomitant Medications

All concomitant medications must be recorded in the subject's CRF according to Section 7.5 and per the Schedule of Events (Appendix 1).

9.5 Unscheduled Visit for Safety

An UNS Visit should be performed if there are suspected subject safety concerns. Procedures for the visit will depend on the reason for visit as determined by the treating principal investigator or sub-investigator. If an UNS Visit is performed because of a safety concern related to study treatments, at a minimum, the following should be performed:

- A targeted physical examination based on subject-reported symptoms including measurement of vital signs (heart rate, blood pressure, respiratory rate, and temperature). For additional details, see Section 9.4.1 and Section 9.4.2.

9.6 Duration of Follow-up

All subjects should be followed for at least 28 days after administration of the study vaccine. If a subject is discontinued early from the study, an Early Discontinuation/EOS assessment should be conducted not earlier than 28 days after the last administration of study vaccine (Section 9.7).

9.7 Early Discontinuation/End of Study

An EOS Assessment is required at Week 56 (Day 393) in alignment with the protocol, GCP as defined in International Council for Harmonisation (ICH) guidelines and US Code of Federal Regulations (CFR), and applicable local regulatory requirements. The EOS procedures will be performed as an Early Discontinuation assessment at least 28 days after the last study injection if the subject is permanently discontinued early from the trial. Investigators are responsible for monitoring the safety of subjects throughout the course of the study and for providing appropriate medical care. The investigator will perform all tasks directly or is responsible for overseeing and training qualified site personnel as delegated to perform study tasks. In addition, investigators are responsible for alerting Dynavax to any event that seems unusual and for reporting all AEs, SAEs, pregnancies, and deaths in the appropriate CRFs.

10 ADVERSE EVENTS

10.1 Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study treatment.

Medical conditions present at Screening (ie, before informed consent is obtained) or present before the study vaccine injection (Day 1) are not AEs and are not recorded on the AE CRF. These medical conditions should be adequately documented on the Medical History CRFs. Any increase in severity or frequency of a medical condition documented as medical history after the study vaccine injection will be recorded as an AE and will be captured on the AE CRF.

Post-injection reactions (Section 10.2) persisting beyond 7 days after each study injection are considered to be AEs and need to be recorded and reported as AEs. These will be included in the electronic data capture (EDC) AE dataset.

If a PIR is inadequately recorded by the subject in the e-diary and occurred during the diary period from Day 1 through Day 7 following each study injection, the investigator can retrospectively evaluate and report at their discretion (as a health care provider), as necessary, through the date of onset on the AE CRF page. These data will be included in the EDC AE dataset.

An uncomplicated pregnancy is not an AE or SAE and should not be reported as an AE/SAE. Subjects should be followed as described in Section 10.9.

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

The investigator will follow all related non-serious AEs observed during the study until the AEs are considered resolved or until EOS. Dynavax or the Dynavax designee may request additional follow-up on specific unresolved events.

AEs should be documented in terms of a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

Any Grade 3 (severe) solicited or unsolicited AE that is considered possibly or probably related to treatment must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event.

10.2 Definition of Post-Injection Reactions

Post-injection reactions persisting beyond 7 days after injection are considered to be AEs and need to be recorded and reported as AEs. The severity of the post-injection reactions will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 2).

Certain local and systemic events are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of systemic nature, may under certain circumstances, in an individual subject, have a cause that is unrelated to study vaccine. However, as a matter of convenience and in accordance with common clinical practice, such events occurring within a specified period of time after immunization are herein termed 'post-injection reactions' and will be considered as related to treatment.

Post-injection reactions documented by the subject will be collected via a diary, reviewed by the study nurse/coordinator with the subject and recorded appropriately.

10.3 Overdoses

If an AE is associated with or resulted from an overdose of study vaccine (for the purpose of this study defined as more than twice the protocol-specified dose), it will be documented on the AE CRF. If it is an SAE, it will also be reported to Dynavax or the Dynavax designee following the SAE reporting process (see Section 10.9.2).

10.4 Adverse Events Associated With Cancer

If an AE is associated with or resulted from cancer, it will be documented on the AE CRF. If it is an SAE, it will also be reported to Dynavax or the Dynavax designee following the SAE reporting process (see Section 10.9.2).

10.5 Definition of Adverse Reaction

An adverse reaction (AR) is defined as any AE caused by the use of a pharmaceutical product. ARs are a subset of all suspected AEs for which there is reason to conclude that the pharmaceutical product caused the event.

10.6 Definition of Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the study treatment caused the AE. *Reasonable possibility* means there is evidence to suggest a causal relationship between the study treatment and AE. An SAR implies a lesser degree of certainty about causality than AR, which means an AE caused by a study treatment.

10.7 Definition of Unexpected Adverse Event or Unexpected Suspected Adverse Reactions

An AE or SAR is considered *unexpected* if it is not listed in the Investigator's Brochure or the approved product label or is not listed at the specificity or severity that has been previously observed.

10.8 Definition of Immune-mediated Adverse Event of Special Interest

Immune-mediated adverse events of special interest (imAESI) are defined according to a pre-specified list of event terms including autoimmune, autoinflammatory, and hypersensitivity disorders (Appendix 3). Each subject will be assessed for AESIs during the entire trial.

10.9 Serious Adverse Events

10.9.1 Definition of Serious Adverse Events

An AE is considered an SAE if it meets any of the following criteria:

- Results in death
- Is life-threatening

  Note: An AE or SAR 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 SAR that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability or incapacity

  That is, the event severely or permanently disrupts the subject's ability to perform normal life functions or daily activities.
- Results in a congenital anomaly or birth defect
- Is medically significant (Important Medical Event)

  Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject. Examples of such events are allergic bronchospasm requiring treatment in an emergency room, serious blood dyscrasias, or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Note: Elective surgery is not an SAE. Additionally, an Emergency Room visit does not fulfill the criteria of hospitalization by definition of an SAE.

10.9.2 Serious Adverse Event Reporting Requirements

Any SAEs, including serious imAESIs, that occur from the time of signed consent through the EOS Visit, whether or not the SAE is related to the study vaccine **must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event**. The contact information for reporting SAEs will be provided to each site. General SAE reporting instructions are as follows:

- Submit SAE documents according to instructions provided.
- Record all SAEs on the AE CRF.
- For SAEs, record the primary event on the AE CRF; describe events occurring secondary to that primary event on the SAE form in the narrative description of the case.
- Death is an outcome, not an event. Record the event that resulted in the death as the fatal event on the AE CRF.
- For hospitalizations for surgical or diagnostic procedures, record the illness leading to the surgical or diagnostic procedure as the SAE, not the procedure itself. Capture the procedure in the narrative as part of the action taken in response to the illness.
- Elective hospitalizations will not be considered SAEs and do not need to be reported. Complications that prolong elective hospitalizations should be recorded as SAEs. Emergency room visits of less than 24 hours do not meet the criterion of hospitalization for SAE reporting purposes.

The SAE report should contain, at a minimum, the following information:

- Subject identifiers (ie, subject number)
- Suspected medicinal product
- AE term (must be listed as serious)
- Contact information for person reporting event

The relationship of the SAE to study vaccine will be assessed by the investigator (Section 10.2). Follow-up information should be actively sought and submitted as it becomes available.

The investigator will assess relationship to study treatment. In addition, the sponsor will assess relationship to study treatment and determine expectedness to study vaccine based on the current study vaccine Investigator's Brochure and USPI. The sponsor will report all study vaccine suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as expedited reports in accordance with applicable regulatory requirements (eg, 21 CFR 312.32[c] and 314.80[e] in the US). All other SAEs will be reported as part of regulatory safety updates, as required, such as in annual reports.

10.10 Adverse Event Severity and Relationship to Study Treatment

10.10.1 Severity Grading of Adverse Events and Abnormal Laboratory Test Results

The severity of AEs and laboratory abnormalities will be graded based on 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 in Appendix 2, 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 10-1.

Table 10-1: 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
Grade 3 – Severe	Prevents daily activity and requires medical intervention
Grade 4 – Potentially life-threatening	Emergency room visit or hospitalization
Grade 5	Death

CBER = Center for Biologics Evaluation and Research.

For all AEs and SAEs, if there is a change in the severity after the event onset, the event should be reported as a single entry with the maximum severity grading captured.

10.10.2 Relationship of Adverse Events to Study Treatment

The investigator will determine the relationship of the AE to study vaccine using the definitions provided in Table 10-2.

Table 10-2: Definitions for Relationship of Adverse Events to Study Treatment

Relationship to Study Vaccine	Definition
Not Related	Another cause of the event is most plausible; *or* clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; *or* a causal relationship is considered biologically implausible.
Possibly Related	An event that follows a reasonable temporal sequence from administration of the study treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.
Probably Related	An event that follows a reasonable temporal sequence from administration of the study treatment, *and* there is a biologically plausible mechanism for study treatment causing or contributing to the AE, *and* the event could not be reasonably explained by the known characteristics of the subject's clinical state. In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

AE = adverse event.

If the SAE is assessed as possibly or probably related to study vaccine, the SAE must be followed until it is considered resolved, chronic or stable, including beyond EOS.

Any SAE assessed as not related to study vaccine will be followed as clinically indicated until its resolution or, if non-resolving, until it is considered chronic or stable, or until 28 days after the last study vaccine injection or until EOS.

The sponsor may request additional follow-up on specific unresolved AEs.

10.11 Reporting and Documentation of Pregnancy and Exposure during Breastfeeding

Any subject who becomes pregnant will be followed to pregnancy outcome even until after study conclusion. Subjects who begin breastfeeding during the study will be followed to EOS or 28 days after last study injection. Follow-up information should be actively sought by the investigator and submitted to Dynavax or designee as soon as it becomes available. The investigator will complete the pregnancy reporting form and all other relevant eCRFs. Uncomplicated pregnancies are not considered an AE/SAE. A complicated pregnancy or a pregnancy with an adverse outcome may meet criteria for an AE or SAE and would then also be reported according to the appropriate requirements.

A subject who becomes pregnant will be instructed to report the pregnancy to the study site as soon as possible. The subject should be followed by the investigator through the pregnancy for safety assessments and pregnancy outcome (including beyond EOS). A report of the pregnancy will be completed by the investigator or designee and will document details of the pregnancy, outcome of pregnancy, and details of delivery.

Pregnancies and breastfeeding that occur from Day 1 through EOS or 28 days after the last administration of the study vaccine must be reported by the investigator. The sponsor or designee must be notified as soon as possible once the study site learns of a pregnancy or breastfeeding. Pregnancy report forms provided by the sponsor or designee must be completed and **reported to Dynavax or its designee within 24 hours of investigator awareness of the event**.

11 STATISTICAL METHODS

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 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. No multiplicity adjustments are made, and all statistical tests will be conducted at 5% two-sided Type I level unless otherwise specified.

All analyses of demographics, medical history, 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. No specific safety hypotheses will be tested.

11.1 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] titer 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 in Part 2 of the study to evaluate the 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 and Phase 2b 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 11-1 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 11-1: 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.

11.2 Study Analysis Populations

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.

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 (to be specified in the statistical analysis plan), and have immunogenicity data obtained within the study visit window at Day [redacted].

Further details of statistical considerations are provided in a separate Statistical Analysis Plan.

11.3 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.

11.4 Immunogenicity Endpoints

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.

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 8 after 2 doses of rF1V vaccine with CpG 1018 as that at Week 30 after 3 doses of rF1V vaccine without CpG 1018

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]

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.

[redacted]

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

Data from Part 1 subjects and Part 2 subjects will be combined to evaluate the Part 2 objectives. No multiplicity adjustment is proposed as the Part 1 objectives are not evaluated against the 3-dose regime control group.

11.5 Safety Analyses

Safety data will be analyzed descriptively and will be based on the Safety Population. Summary statistics will be used to describe the incidence of all post-injection reactions, AEs, AESIs, SAEs, and deaths. Tables of adverse events will include incidence, severity, seriousness, and relationship to the investigational vaccines.

11.6 Interim Analysis

This study has no planned interim analysis.

12 DATA QUALITY ASSURANCE

The study sites will be monitored by Dynavax or its designee according to GCP and standard operating procedures. Prior to initiation of the study, representatives from Dynavax or its designee will review with the site personnel information about the investigational product, proper storage of study treatments, protocol requirements, and monitoring requirements. During and after the study, periodic on-site and remote visits will be conducted to monitor for compliance, including verification of the accuracy and completeness of data recorded on the CRFs, source documents, and study treatments accountability records.

13 ETHICS

The protocol and informed consent documents must be reviewed and approved by an appropriately composed Institutional Review Board (IRB). The study will not be initiated at a site until appropriate written IRB approval of the protocol, ICF, and all recruiting materials (if applicable) is obtained by the investigator. Copies should be reviewed and approved by Dynavax prior to submission to the IRB. The investigator will submit periodic reports on the progress of the study as required by the IRB, in accordance with applicable governmental regulations, and in agreement with the policy established by Dynavax. In addition, the investigator will inform the IRB of any protocol amendments and administrative changes and will obtain appropriate written IRB approval of all protocol amendments.

13.1 Ethical Conduct of the Study

This study will be conducted in accordance with the protocol; GCP as defined in International Council for Harmonisation (ICH) guidelines and US CFR Title 21, Parts 11, 50, 54, 56, 312, and Title 45 Parts 46, 160 and 164; the EU Directives 2001/20/EC and 2005/28/EC; the Declaration of Helsinki (1989); IRB Guidelines; and applicable local legal and regulatory requirements.

13.2 Informed Consent

The investigator is responsible for maintaining the privacy and confidentiality of the subject's medical or health information collected during the in compliance with US CFR Title 21 Part 50, Title 45 Part 46 and ICH and IRB guidelines. Prior to initiation of the study at the site, the ICF form must be reviewed and accepted by Dynavax and approved by the governing IRB. The investigator or authorized designee will discuss the purpose and pertinent details of the study with each subject, and the subject must understand, sign, and date the appropriate IRB-approved ICF before undergoing any study-specific procedures. The ICF must be personally signed and dated by the subject and by the person who conducted the informed consent discussion. Additional signature requirements may exist. The original signed and dated ICF will be retained with the subject's study records, and a copy of the signed ICF will be made available to the

subject. The investigator or designee will maintain a log of all subjects who sign the ICF. Screening log content is described in Section 9.1.1.

13.3 Subject Confidentiality

The investigator is responsible for maintaining the privacy and confidentiality of the subject's medical or health information collected during the study. The investigator is also responsible for ensuring that all use, review, and disclosure of subject's medical or health information is in accordance with the Health Insurance Portability and Accountability Act (HIPAA) regulations and with local/regional requirements and that the ICF is approved by the IRB and signed by the subject.

13.4 Data Handling and Record Keeping

13.4.1 Source Documents

The investigator must maintain detailed records of all study subjects who are enrolled in the study or who undergo screening. Source documents include, but are not limited to, subject medical records and investigator's subject study files, as well as all test results.

The following minimum information should be entered into the enrolled subject's source documents:

- The date the subject entered the study (received study injection) and the subject number
- The study protocol number and the name Dynavax Technologies or Dynavax
- The date that informed consent/assent was signed/obtained
- Evidence that informed consent/assent was obtained before the subject underwent any study-specific procedures
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures, evaluations)
- The dates of all study-related subject visits
- Evidence that study-required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of study drug accountability
- Subject e-diary (or equivalent) entries
- Occurrence and status of any AEs
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued early, including the reason for discontinuation
- Any deviations from the protocol

13.4.2 Direct Access to Source Data/Documents

Qualified individuals designated by Dynavax or its representative will monitor all aspects of the study at regular intervals throughout the study and following study completion. This monitoring is for the purpose of verifying adherence to the protocol including appropriate storage of study treatment, completeness and exactness of the data being entered onto the CRFs, and compliance with FDA or other regulatory agency regulations. The investigator and investigator's institution agree to allow these monitors access to all study records, CRFs, and corresponding portions of the subject's clinical study files; to allow access to the clinical supplies, dispensing, and storage areas; and if requested, to assist the monitors. The investigator further agrees to permit direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection(s).

In certain circumstances, a secondary audit may be conducted by members of Dynavax's Clinical Quality Assurance group or by Dynavax's designated representative. The investigator will be notified if this is to take place and advised as to the nature of the audit.

13.5 Case Report Forms

Case report forms (CRFs) will be used at the clinical study site to collect study data for enrolled subjects. For screen failures, the sponsor will collect, at a minimum, age, sex, ethnicity, race, the reason for screen failure and any SAEs that occur during the screening period.

When data are available, authorized clinical study site personnel will carefully and accurately record the data on the CRFs. Sites must ensure that all source documents are maintained according to ICH/GCP guidance and support the data that are entered onto the CRFs.

Case report forms will be in electronic form (eCRFs) for this study. The eCRF data will be captured in a system validated according to procedures that comply with 21 CFR Part 11, and ICH Guidelines for GCP E6 (R2), November 2016, Section 5.5. The eCRFs will be reviewed and signed by the principal investigator or someone clinically qualified and identified on the delegation log as someone that can sign-off on the eCRF.

13.6 Data Handling

The sponsor may designate a Contract Research Organization (CRO) to perform data management. The CRO will write a data management plan outlining the data management systems, procedures, and agreements between the CRO and sponsor. The plan will be reviewed and signed by a representative of the sponsor's data management department.

Outside the electronic data capture (EDC) system, when appropriate, the sponsor or designee (CRO) will receive FDA 21 CFR Part 11 (or locally required equivalent) compliant external lab data transfers from a validated laboratory information management system and subject reported safety information from a validated electronic patient report outcome (ePRO) system.

After database lock, the investigator will receive a copy of the subject data for archiving at the study site.

Validation checks will be conducted to capture data errors, and data clarification queries will be generated at the time of data monitoring. Validation checks and queries will be issued to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

Data verification against the source documents will be performed by the sponsor or its designee prior to locking of the study database. Following the completion of source data verification, a thorough review of data will be completed manually by the clinical data managers to ensure data consistency and to identify and request correction of any remaining data errors. All queries will be resolved or closed with written documentation providing reasons for irresolvable queries. Additional manual validation checks will be performed as needed.

13.7 Coding of Adverse Events, Drugs, and Diseases

AEs and medical histories will be coded using a current version of the MedDRA. Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary.

13.8 Record Retention

The investigator must retain all records relating to the conduct of this study (including subject's study records, receipt and disposition of all investigational materials, subject exclusion logs, signed consent forms, eCRFs, all correspondence, and other supporting documentation) for at least 2 years after a marketing application for this indication is approved; or if an application is not filed or not approved for the drug for this indication, for at least 2 years after clinical development for the drug has been formally discontinued and the appropriate regulatory or health authorities have been notified. However, in certain instances, documents may need to be retained for a longer period if required by regulatory requirements or by an agreement with Dynavax.

The investigator may withdraw from the responsibility of retaining records only after transferring custody of the records to another individual who will accept responsibility for them. A written notice of transfer must be provided to Dynavax prior to or no later than 10 days after transfer.

The investigator must allow representatives of the FDA, the governing IRB, or other regulatory agencies to inspect all study records. If informed of such an inspection, the investigator will notify Dynavax within 24 hours of being informed.

The investigator must obtain written approval from Dynavax prior to the destruction of any records relating to the conduct of this study.

14 USE OF INFORMATION AND PUBLICATION

No information related to data obtained and generated in this study shall be released or publicized without the prior written consent of an Agreements Officer Representative of the U.S. Government.

Any publication will have the following statement to acknowledge the support of the Government whenever publicizing the study in any media:

This project has been funded in part by the U.S. Government under Agreement W911QY-21-9-0018. The US Government is authorized to reproduce and distribute reprints for Governmental purposes notwithstanding any copyright notation thereon.

15 REFERENCES

Arunachalam, P. S., A. C. Walls, N. Golden, C. Atyeo, S. Fischinger, C. Li, P. Aye, M. J. Navarro, L. Lai, V. V. Edara, K. Röltgen, K. Rogers, L. Shirreff, D. E. Ferrell, S. Wrenn, D. Pettie, J. C. Kraft, M. C. Miranda, E. Kepl, C. Sydeman, N. Brunette, M. Murphy, B. Fiala, L. Carter, A. G. White, M. Trisal, C.-L. Hsieh, K. Russell-Lodrigue, C. Monjure, J. Dufour, S. Spencer, L. Doyle-Meyer, R. P. Bohm, N. J. Maness, C. Roy, J. A. Plante, K. S. Plante, A. Zhu, M. J. Gorman, S. Shin, X. Shen, J. Fontenot, S. Gupta, D. T. O'Hagan, R. Van Der Most, R. Rappuoli, R. L. Coffman, D. Novack, J. S. McLellan, S. Subramaniam, D. Montefiori, S. D. Boyd, J. L. Flynn, G. Alter, F. Villinger, H. Kleanthous, J. Rappaport, M. S. Suthar, N. P. King, D. Veesler and B. Pulendran (2021). "Adjuvanting a subunit COVID-19 vaccine to induce protective immunity." Nature.

Center for Biologics Evaluation and Research (2007). Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, Food and Drug Administration.

Daya, M. and Y. Nakamura (2005). "Pulmonary disease from biological agents: anthrax, plague, Q fever, and tularemia." Crit Care Clin **21**(4): 747-763, vii.

Dynavax Technologies Corporation (2021). HEPLISAV-B SmPC.

Dynavax Technologies Corporation, P. I. (2020). "HEPLISAV-B® Package Insert."

Halperin, S. A., B. Ward, C. Cooper, G. Predy, F. Diaz-Mitoma, M. Dionne, J. Embree, A. McGeer, P. Zickler, K. H. Moltz, R. Martz, I. Meyer, S. McNeil, J. M. Langley, E. Martins, W. L. Heyward and J. T. Martin (2012). "Comparison of safety and immunogenicity of two doses of investigational hepatitis B virus surface antigen co-administered with an immunostimulatory phosphorothioate oligodeoxyribonucleotide and three doses of a licensed hepatitis B vaccine in healthy adults 18-55 years of age." Vaccine **30**(15): 2556-2563.

Hart, M. K., G. A. Saviolakis, S. L. Welkos and R. V. House (2012). "Advanced Development of the rF1V and rBV A/B Vaccines: Progress and Challenges." Advances in preventive medicine **2012**: 731604-731604.

Heyward, W. L., M. Kyle, J. Blumenau, M. Davis, K. Reisinger, M. L. Kabongo, S. Bennett, R. S. Janssen, H. Namini and J. T. Martin (2013). "Immunogenicity and safety of an investigational hepatitis B vaccine with a Toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40-70 years of age." Vaccine **31**(46): 5300-5305.

Hinnebusch, B. J. and D. L. Erickson (2008). "Yersinia pestis biofilm in the flea vector and its role in the transmission of plague." Curr Top Microbiol Immunol **322**: 229-248.

Hsieh, S.-M., M.-C. Liu, Y.-H. Chen, W.-S. Lee, S.-J. Hwang, S.-H. Cheng, W.-C. Ko, K.-P. Hwang, N.-C. Wang, Y.-L. Lee, Y.-L. Lin, S.-R. Shih, C.-G. Huang, C.-C. Liao, J.-J. Liang, C.-

S. Chang, C. Chen, C. E. Lien, I.-C. Tai and T.-Y. Lin (2021). "Safety and Immunogenicity of CpG 1018 and Aluminium Hydroxide-Adjuvanted SARS-CoV-2 S-2P Protein Vaccine MVC-COV1901: A Large-Scale Double-Blinded, Randomised, Placebo-Controlled Phase 2 Trial." medRxiv: 2021.2008.2005.21261532.

Hsieh, S.-M., M.-C. Liu, Y.-H. Chen, W.-S. Lee, S.-J. Hwang, S.-H. Cheng, W.-C. Ko, K.-P. Hwang, N.-C. Wang, Y.-L. Lee, Y.-L. Lin, S.-R. Shih, C.-G. Huang, C.-C. Liao, J.-J. Liang, C.-S. Chang, C. Chen, C. E. Lien, I. C. Tai and T.-Y. Lin (2021). "Safety and immunogenicity of CpG 1018 and aluminium hydroxide-adjuvanted SARS-CoV-2 S-2P protein vaccine MVC-COV1901: interim results of a large-scale, double-blind, randomised, placebo-controlled phase 2 trial in Taiwan." The Lancet Respiratory Medicine **9**(12): 1396-1406.

Hsieh, S.-M., W.-D. Liu, Y.-S. Huang, Y.-J. Lin, E.-F. Hsieh, W.-C. Lian, C. Chen, R. Janssen, S.-R. Shih, C.-G. Huang, I. C. Tai and S.-C. Chang (2021). "Safety and immunogenicity of a Recombinant Stabilized Prefusion SARS-CoV-2 Spike Protein Vaccine (MVC COV1901) Adjuvanted with CpG 1018 and Aluminum Hydroxide in healthy adults: A Phase 1, dose-escalation study." EClinicalMedicine **38**: 100989.

Hyer, R., D. K. McGuire, B. Xing, S. Jackson and R. Janssen (2018). "Safety of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant in adults." Vaccine **36**(19): 2604-2611.

Inglesby, T. V., D. T. Dennis, D. A. Henderson, J. G. Bartlett, M. S. Ascher, E. Eitzen, A. D. Fine, A. M. Friedlander, J. Hauer, J. F. Koerner, M. Layton, J. McDade, M. T. Osterholm, T. O'Toole, G. Parker, T. M. Perl, P. K. Russell, M. Schoch-Spana and K. Tonat (2000). "Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense." Jama **283**(17): 2281-2290.

Jackson, S., J. Lentino, J. Kopp, L. Murray, W. Ellison, M. Rhee, G. Shockey, L. Akella, K. Erby, W. L. Heyward and R. S. Janssen (2018). "Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults." Vaccine **36**(5): 668-674.

Khoury, D. S., D. Cromer, A. Reynaldi, T. E. Schlub, A. K. Wheatley, J. A. Juno, K. Subbarao, S. J. Kent, J. A. Triccas and M. P. Davenport (2021). "Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection." Nature Medicine **27**(7): 1205-1211.

Koirala, J. (2006). "Plague: disease, management, and recognition of act of terrorism." Infect Dis Clin North Am **20**(2): 273-287, viii.

McGovern, T. F., A.M. (1997). Plague. Medical Aspects of Chemical and Biological Warfare. Washington, DC, USA, US Department of the Army, Office of the Surgeon General, and Borden Institute**:** 479–502.

Perry, R. D. and J. D. Fetherston (1997). "Yersinia pestis--etiologic agent of plague." Clin Microbiol Rev **10**(1): 35-66.

Prentice, M. B. and L. Rahalison (2007). "Plague." Lancet **369**(9568): 1196-1207.

Richmond, P., L. Hatchuel, M. Dong, B. Ma, B. Hu, I. Smolenov, P. Li, P. Liang, H. H. Han, J. Liang and R. Clemens (2021). "Safety and immunogenicity of S-Trimer (SCB-2019), a protein subunit vaccine candidate for COVID-19 in healthy adults: a phase 1, randomised, double-blind, placebo-controlled trial." The Lancet **397**: 682-694.

Richmond, P. C., L. Hatchuel, F. Pacciarini, B. Hu, I. Smolenov, P. Li, P. Liang, H. H. Han, J. Liang and R. Clemens (2021). "Persistence of the Immune Responses and Cross-Neutralizing Activity With Variants of Concern Following 2 Doses of Adjuvanted SCB-2019 Coronavirus Disease 2019 Vaccine." The Journal of Infectious Diseases.

Vadyvaloo, V., C. Jarrett, D. Sturdevant, F. Sebbane and B. J. Hinnebusch (2007). "Analysis of Yersinia pestis gene expression in the flea vector." Adv Exp Med Biol **603**: 192-200.

APPENDIX 1: SCHEDULE OF TRIAL EVENTS

	Screen-ing[a]	Treat-ment	Follow up	Treat-ment	Follow up			Treat-ment	Follow up			EOS/ Early Discontinuation[b] (TC)
Days												393 (±14) (Early discontinuation: 28 days after last study vaccine)
Weeks												
												13
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics[e]	X											
Medical and Medication History[e]	X	X										
Vital Signs [f]	X	X		X				X				
Physical Exam[g]	X											
HIV, HBV, HCV Testing[h]	X											
Pregnancy test [i]	X			X				X				
Serum chemistry[k]	X			X								
Hematology[l]	X			X								
Blood sample for rF1V concentration[m]		X			[d] X	X	X		X	X	X	
Blood samples for reserve/exploratory objectives[n]	X	X			X	X	X	X				
Study injections for rF1V vaccine and CpG 1018[o]		X						X				
Study injections for rF1V vaccine and placebo[o]		X						X				
30-minute post-injection observation[p]		X						X				
Distribute and/or Review Subject e-Diary or equivalent) Instructions		X						X				
Review Subject e-Diary (or equivalent) with Daily Temperature and Local/Systemic Reactions [j]		X						X				
Assessment of AEs, SAEs, immune-mediated AESIs [q,r]	X[r]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BP = blood pressure; CBC = complete blood count; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; RR = respiratory rate; SAE = serious adverse event; TC= telephone call.

APPENDIX 1: SCHEDULE OF TRIAL EVENTS (CONT'D) FOOTNOTES

Screening[a]	Routine laboratory tests (serum chemistry, hematology) for screening should be performed within 28 days prior to enrollment. Subjects may have the screening window extended an additional 7-calendar days if they have equivocal laboratory results or if they cannot be enrolled during the screening window. The screening window may only be extended one time and must have prior approval by the sponsor's medical monitor.
EOS/Safety F/U[b]	A mandatory EOS/Safety Follow-up telephone call will be performed [redacted] after the administration of the last study vaccine. If a subject receives received less than 3 doses of vaccine, their EOS visit will be 28 days after their last dose. The EOS visit procedures will be performed as an Early Discontinuation visit if the subject is permanently discontinued early from the trial.
Telephone Call[c]	Telephone call Day 4 (Part 1 only) and EOS
Part 1 Final immunogenicity Assessment[d]	Part 1 final immunogenicity assessment will be conducted based on Day 57.
Demographics/Medical History/Prior Medications[e]	Demographic and baseline characteristics of sex, race, ethnicity, age, weight, and height, and medical history will be collected. Report complete medication history for 28 days prior to Baseline (Day 1).
Vital Signs[f]	Includes oral temperature (only at trial injection visits), heart rate, respiratory rate, systolic and diastolic blood pressure.
Physical Examination[g]	The investigator or qualified designee will conduct physical examinations. A complete physical examination is conducted at Screening. A symptom-directed physical exam is conducted at all other designated time points.
HIV, HBV, HCV Testing[h]	HIV, HBV, HCV testing.
Pregnancy Test[i]	For females of childbearing potential, a serum pregnancy test will be collected at screening and must be negative for the subject to participate. A urine pregnancy test must be negative within 24 hours prior to administration of each study vaccine. The test must be negative for the subject to receive study injection.
Subject Diary[j]	At the Day 1 visit, subjects are provided with a ruler, thermometer and instructions for completing the study diary. At Day [redacted] subjects are instructed to complete the e-diary (or equivalent) to record any solicited local (pain, pruritus, redness, and swelling at the injection site) and solicited systemic signs and symptoms (fatigue, chills, myalgia, malaise, fever, gastrointestinal symptoms, and headache) during the 7-day follow-up period after administration of each study vaccine.
Serum Chemistry[k]	Chemistry (includes sodium, potassium, chloride, bicarbonate, BUN, Cr, glucose, calcium, AST, ALT, LDH, bilirubin, alkaline phosphatase).
Hematology[l]	Hematology includes red blood cell count, Hgb, hematocrit, WBC count with differential, and platelet count.
Serology[m]	Standardized enzyme-linked immunosorbent assays [redacted] to determine serum concentrations of antibodies to rF1V. Samples will be drawn prior to study vaccine injection on vaccination days. The same sample will be used for the exploratory analysis to determine serum concentrations of antibodies to rF1 and rV.
Reserve Serum Aliquot[n]	An extra aliquot of serum collected and stored frozen for possible future testing (drawn prior to study injection on vaccine days)
Study Vaccine Administration[o]	Subjects will be randomly assigned and receive an injection of study vaccine on vaccination days. If Group 2 is selected from the Part 1, then in Part 2, placebo will not be co-administered with rF1V.
Post-Injection Observation[p]	Subjects will remain in the clinic for 30 minutes after administration of study vaccine for observation of post-injection local and systemic reactions and AEs.
Review AEs[q]	All AEs will be graded per CBER Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and evaluated for seriousness. AEs will be collected Day 1 through Week 56 or Early Discontinuation Visit.
Review SAEs[r]	All SAEs will be evaluated from the time the consent is signed through the EOS Visit. SAEs must be reported to Dynavax or its designee within 24 hours of the knowledge of the event.

APPENDIX 2: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Local Injection Site) Reactions				
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Pruritus[c]	No interference with activity	Some interference with activity, not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Systemic Reactions				
Fever (°C)	38.0 – 38.4	38.5-38.9	39.0-40	>40
Myalgia	No interference with activity	Some interference with activity	Significant: prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant: prevents daily activity	ER visit or hospitalization
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	*A grade is not available*	*A grade is not available*
Chills[c]	No interference with activity	Some interference with activity, not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
Nausea/ vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms /24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Systemic Illness				
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Source: (Center for Biologics Evaluation and Research 2007).
ER = emergency room; IV = intravenous.
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement
[c] Not part of CBER grading scale.

APPENDIX 3: LIST OF AUTOIMMUNE CONDITIONS AND TERMS OF SPECIAL INTEREST

Any of the conditions listed below that are newly occurring after vaccination are to be categorized as an AESI. In addition, subjects with any of the conditions listed below are excluded from the study[a].

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

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

Metabolic diseases
- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type 1
- Grave's or Basedow's disease

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

Neuroinflammatory disorders

- Acute disseminated encephalomyelitis, including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis
- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Tolosa Hunt syndrome[b]
- Immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)
- Multiple sclerosis
- Myasthenia gravis, including Eaton-Lambert syndrome
- Narcolepsy
- Optic neuritis
- Transverse Myelitis

Skin disorders

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

Vasculitides

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

Others

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

[a] List provided to Dynavax Technologies by FDA on 30 January 2019
[b] Added by Dynavax