Official Protocol Title:	A Phase I Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of V160 (Human Cytomegalovirus Vaccine) in Healthy Japanese Men
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Title Page

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Protocol Title: A Phase I Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of V160 (Human Cytomegalovirus Vaccine) in Healthy Japanese Men

Protocol Number: 003-00

Compound Number: V160

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

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Regulatory Agency Identifying Number(s):

IND	Not Applicable

Approval Date: 19-November-2018

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase I Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of V160 (Human Cytomegalovirus Vaccine) in Healthy Japanese Men

Short Title: Phase I Study for Safety and Immunogenicity of V160 in Healthy Japanese Men

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for the study.

The following objectives will be evaluated in healthy Japanese male participants 20 years to 64 years of age inclusive.

Primary Objectives	Primary Endpoints
To assess the safety and tolerability of a 3-dose regimen of V160 administered intramuscular (IM) by cytomegalovirus (CMV) serostatus.	- Solicited injection site adverse events (AEs) within Days 1 through 5 after each vaccination visit, and solicited systemic AEs, and vaccine-related serious adverse events (SAEs) within Days 1 through 14 after each vaccination visit
Secondary Objectives	Secondary Endpoints
To evaluate CMV-specific neutralizing antibody (NAb) geometric mean titers (GMTs) at 1 month postdose (PD)3 in initially CMV-seronegative participants vaccinated with a 3-dose regimen of V160 administered IM.	- CMV-specific NAb titers
To evaluate viral detection, viral shedding, and viral leakage of V160 by the number and proportion of the participants with positive viral detection in plasma up to 14 days PD1, in urine and saliva up to 1 month PD3, and in injection-site swab and adhesive tape swab up to 30 minutes PD1 by CMV serostatus.	- Viral detection of V160 in plasma, urine and saliva, and injection-site swab and adhesive tape swab

Overall Design:

Study Phase	Phase 1
Primary Purpose	Prevention
Indication	Prevention of CMV infection in vaccinated women, and congenital CMV infection (cCMVi)/congenital CMV disease (cCMVd) in children born to vaccinated women
Population	Healthy Japanese male, 20 years to 64 years of age inclusive.
Study Type	Interventional
Intervention Model	Parallel This is a single-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Investigator, Participant, and Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 9.5 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result.

Number of Participants:

Approximately 18 participants will be allocated/randomized as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Intervention Name	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin.	Vaccination Regimen	Use
V160	V160	Lyophilized Cake	200 Units/mL	100 Units with 225 µg aluminum per 0.5mL dose	IM	Day 1, Month 2, Month 6	Experimental
	APA Diluent	Sterile Suspension for reconstitution	450 µg/mL				Adjuvant
Placebo	Sterile Saline Placebo	Sterile Solution	Not applicable	0.5 mL	IM	Day 1, Month 2, Month 6	Placebo

Abbreviations: APA Diluent = Aluminum Phosphate Adjuvant (APA) Diluent, Sterile Saline Placebo = V160 Sterile Saline Placebo, Unit Dose Strength = Strength of the V160 and APA product after reconstitution, Dosage level = post reconstitution per 0.5 mL dose, IM = Intramuscular

Total Number	2 intervention groups
Duration of Participation	Each participant will participate in the study for approximately 7.5 months from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 21 days, each participant will be receiving assigned intervention for approximately 6 months. After the end of vaccination each participant will be followed for 1 month.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

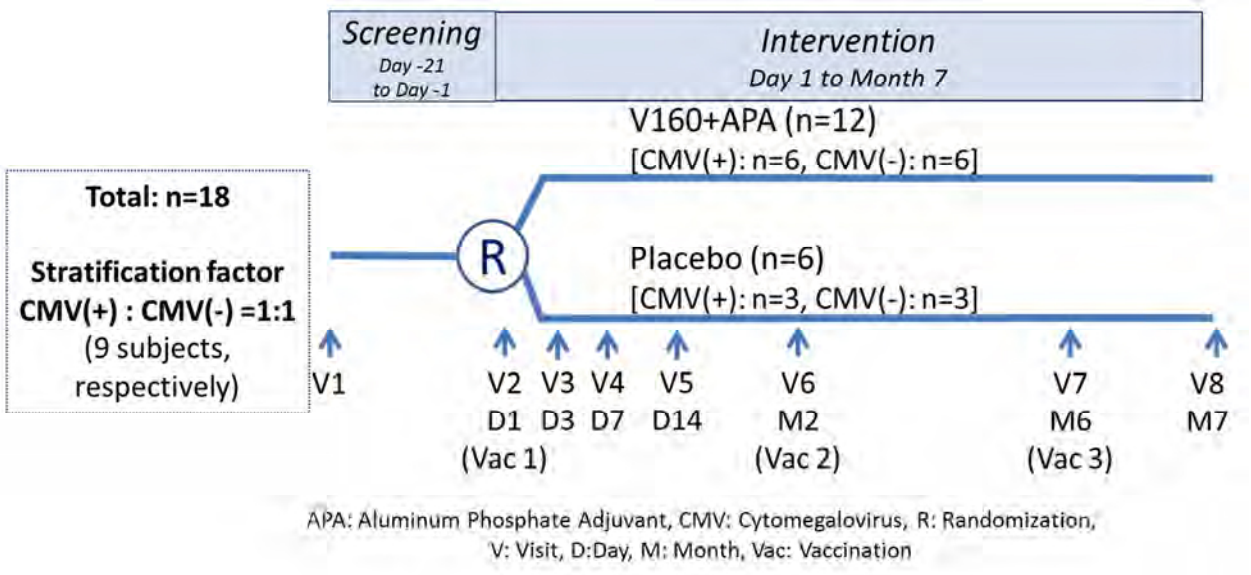


Figure 1 Study Design Diagram

1.3 Schedule of Activities (SoA)

Study Period	Screening	Intervention							Notes
Visit Number/Title	Visit 1 Screening	Visit 2 Day 1 Vac 1	Visit 3	Visit 4	Visit 5	Visit6 Month 2 Vac 2	Visit 7 Month 6 Vac 3	Visit 8 Month 7	
Scheduled Day	-21 to -1	1	3	7	14	60	180	210	
Scheduling Window (Days)	-21 to -1		+/- 1	+/- 2	+/- 2	+14	+14	+14	
Administrative Procedures									
Informed Consent	X								
Informed Consent for Future Biomedical Research	X								
Check Inclusion/Exclusion Criteria	X	X							Performed prior to vaccination
Participant Identification Card	X								
Medical History	X								
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	
Vaccine Randomization		X							
V160/Placebo Administration		X				X	X		
Distribution of VRC		X				X	X		
Review of VRC data			X	X	X	X	X	X	Telephone contacts after 14 days from Month 2 and Month 6, respectively to remind the subjects: See Section 8.3.3.
Check postdose 1 Deferment/ Exclusion/Discontinuation criteria						X	X		Performed prior to vaccination
Collection of VRC						X	X	X	
Clinical Procedures/Assessments									
Full Physical Examination	X								Includes height, weight, vital signs and other assessments specified in Section 8.3.1.
Directed Physical Examination		X				X	X	X	Includes vital signs and limited assessments specified in Section 8.3.1. Performed prior to vaccination for the vaccination visits.
30 Minutes Postdose Observation		X				X	X		

Study Period	Screening	Intervention							Notes
Visit Number/Title	Visit 1 Screening	Visit 2 Day 1 Vac 1	Visit 3	Visit 4	Visit 5	Visit6 Month 2 Vac 2	Visit 7 Month 6 Vac 3	Visit 8 Month 7	
Scheduled Day	-21 to -1	1	3	7	14	60	180	210	
Scheduling Window (Days)	-21 to -1		+/- 1	+/- 2	+/- 2	+14	+14	+14	
AE Monitoring	X	X	X	X	X	X	X	X	Detailed reporting time periods for AEs are indicated in Table 2; See Section 8.4.1.
Laboratory Procedures/Assessments									
Screening for CMV Serostatus by IgG	X								
Blood (DNA) for Future Biomedical Research		X							Collect sample prior to vaccination; See Section 8.8.
Blood(Serum) for Neutralizing Antibody titer		X						X	Collect sample prior to vaccination on Day 1; See Section 8.2.1.
Blood(Plasma) for Viral Assessment		X	X	X	X				Collect samples at 3 points on Day 1; See Section 8.3.4.
Swab Sampling from Injection-site for Viral Assessment		X							Collect samples at 4 points on Day 1; See Section 8.3.4.
Swab Sampling from Adhesive Tape (Inside and Outside, respectively) for Viral Assessment		X							Collect samples from each side at 3 points on Day 1; See Section 8.3.4.
Urine and Saliva Collection for Viral Assessment		X	X	X	X	X	X	X	Collect sample prior to vaccination; See Section 8.3.4.
AE: Adverse Events, CMV:cytomegalovirus, DNA:deoxyribonucleic acid, IgG:immunoglobulin G, Vac:vaccination, VRC:Vaccination Report Card									

2 INTRODUCTION

2.1 Study Rationale

Merck is developing an investigational CMV vaccine (referred to as V160) for the prevention of infection and disease caused by CMV in vulnerable populations. Although CMV infection (CMVi) is asymptomatic in healthy individuals, CMV is an important pathogen for congenitally infected infants and immunosuppressed individuals, such as solid organ transplant or hematopoietic stem cell transplant recipients.

Congenital CMV infection (cCMVi) is the most frequent infectious cause of newborn malformation in developed countries. Congenital CMVi, which can lead to congenital CMV disease (cCMVd), presents as sensorineural hearing loss (responsible for almost one-third of all cases), and neurodevelopmental abnormalities. Congenital CMVd occurs more frequently than Down's syndrome, Spina Bifida, Fetal Alcohol Syndrome and, non-epidemic Congenital Rubella Syndrome (prior to preventing onset of rubella with wide use of a vaccine). Development of a vaccine for prevention of cCMVi has been rated a high priority by the National Academy of Medicine [Institute of Medicine 2000].

V160 is initially being developed worldwide for use in women of childbearing age independent of CMV serostatus. This study is being conducted to evaluate the safety, including biodistribution in human, and immunogenicity of V160 in healthy Japanese men, prior to a planned study in Japanese women of childbearing age in near future.

2.2 Background

Human CMV, also known as human herpesvirus 5 is a double-stranded deoxyribonucleic acid (DNA) virus belonging to the beta-herpesvirus family of Herpesviridae. Acquisition appears to require close or intimate contact with persons who are excreting CMV in their urine, saliva or other secretions. CMV can also be transmitted via blood transfusion, breast milk, sexual intercourse, and transplanted organs.

In most healthy individuals, CMVi is asymptomatic. When symptoms are present, they are often mild, can be confused with other illnesses, and include fever, sore throat, fatigue, and/or swollen glands. After infection, the virus establishes lifelong latency, the evidence of which is the detection of anti-CMV antibodies in the blood (CMV seropositivity). Healthy individuals with latent CMV infection can reactivate to shed the virus in their saliva or urine, which is also predominantly asymptomatic.

It is known that CMV can cause serious disease in congenitally infected newborns and immunocompromised individuals. The spectrum of disease in newborns with cCMVi ranges from fetal/infant death to neurological and sensory impairments which are diagnosed later in childhood [Hahn, G., et al 1998] [Just-Nubling, G., et al 2003] [Sinclair, J. 2008] [Lanzieri, T. M., et al 2014].

Congenital CMVi is a significant public health problem. Following the widespread use of rubella vaccine and the elimination of endemic rubella and congenital rubella syndrome in many developed countries [Reef, S. E, et al 2006], cCMVi is now the most common congenital viral infection in these countries, and is estimated that approximately 0.6%-0.7% will have cCMVi at birth [Dollard, S. C., et al 2007]. Approximately 10%-15% of cCMVi will develop symptoms of central nervous system damage either at birth or progressively in the first few years of life, with clinical manifestations including sensorineural hearing loss, mental retardation, and cerebral palsy [Sung, H., et al 2010]. In Japan, rates of cCMVi have been reported to be approximately 0.3% of the newborns [Koyano 2011]. It was also reported in Japan that 30% of cCMVi had typical clinical manifestations and/or showed abnormalities in brain images at birth [Koyano 2011].

Maternal immunity from naturally acquired infection can protect a fetus from cCMVi. In developed countries, maternal seropositivity/seroprevalence (IgG positivity) for CMV is approximately 50% and the prevalence of cCMVi among infants is estimated to be approximately 0.7% among live births [Dollard, S. C., et al 2007]. In Japan, maternal seropositivity for CMV is approximately 71% in 2009 [Azuma 2010], and seropositivity in women of child bearing age has been decreasing by year [Iida 2015].

Refer to the Investigator's Brochure (IB) for detailed background information on V160.

2.2.1 Pharmaceutical and Therapeutic Background

There is no effective CMV vaccine to protect women from acquiring CMVi during pregnancy or any recognized intervention that can effectively reduce transmission of CMV from newly infected pregnant women to the fetus.

Immune responses to natural CMVi can partially protect individuals against re-infection [Plotkin, S. A., et al 1989] [Adler, S. P., et al 1995]. Maternal immunity from naturally acquired infection can also partially protect a fetus from cCMVi [Fowler, K. B., et al 2003]. In addition, CMV-seropositivity is associated with a lower incidence of severe CMV disease post-transplantation [Opelz, G., et al 2004] [Griffiths, P. D., et al 2011]. An effective CMV vaccine could therefore be designed to parallel the immune response commonly seen in healthy CMV seropositive individuals and should induce both humoral and cellular immunity [Wang, D., et al 2016]. Such a vaccine could protect women from acquisition of CMVi, and thereby prevent vertical transmission to their baby, and would be a major medical advance that addresses a critical unmet public health need.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Preclinical Studies

The AD169 strain of CMV was originally isolated at the National Institutes of Health from the adenoids of a 7-year-old girl. The isolate was attenuated through multiple passages in human fibroblasts. This live attenuated virus was tested as a vaccine in a Phase-1 study in 24 CMV seronegative male participants [Neff, B. J., et al 1979]. The vaccine was well tolerated

and did not cause any serious adverse events (SAEs). No virus could be recovered either from peripheral lymphocytes or urine of the vaccinated participants.

The V160 vaccine was created using the Merck variant of AD169 virus (MAD169). The vaccine virus was genetically modified to be conditionally replication defective in the absence of a synthetic molecule called Shield-1 through the ddFKBP-mediated destabilization of two viral proteins critical for viral replication. With Shield-1 present, viral stocks for V160 can be grown; but in vivo with no Shield-1, replication of V160 is prevented. In order to facilitate broad immune responses, the pentameric complex (gH/gL/pUL128-131) was restored on the V160 virus. This restores elicitation of antibodies against the gH antigens, as well as viral tropism of V160 for epithelial and endothelial cells, permitting entry and some protein production without replication (in the absence of Shield-1). Cell-mediated and humoral antibody responses are thereby enhanced.

Since there is no relevant animal model available to assess CMV vaccine efficacy, the key immunological parameters for preclinical evaluations were based on neutralizing antibodies (NAbs) and T-cell responses in animals. V160 has been extensively evaluated in rhesus macaques, and can elicit potent NAbs superior to those seen with the gB/MF59 candidate CMV vaccine as well as balanced CD4 and CD8 T cell responses. V160 was well tolerated in toxicology studies in animals, which supports the administration of this vaccine to humans.

A biodistribution study in rats was conducted to investigate the distribution of V160 to blood and tissues after vaccination. The results of this study demonstrated that V160 was reported as negative in any samples collected just after injection through 1 month, except for IM injection site samples. The V160 strain at IM injection site disappeared at a month after vaccination.

2.2.2.2 Clinical Studies

Phase 1 Clinical Study

The first-in-human study was a Phase 1 dose ranging study to assess the safety and immunogenicity of various antigen dose levels, formulations, and routes of administration in healthy volunteers 18 years of age and older (V160-001) in United States. In study V160-001, the safety and tolerability as well as the immunogenicity of V160 was evaluated in both CMV seronegative and seropositive participants and is briefly summarized below. Refer to the IB for more detailed information.

Participants in study V160-001 received a 3-dose vaccination regimen (0-1-6 month schedule) at various doses (10-250 units) administered intramuscularly or intradermally, with and without aluminum phosphate adjuvant. A saline placebo was used as the control.

In initially CMV seronegative participants, all vaccination groups receiving V160 with and without aluminum phosphate adjuvant exhibited statistically significant higher CMV-specific NAb titers compared with the placebo group. The NAb geometric mean titer (GMT) at Month 7 was highest in recipients of V160 100 unit dose + aluminum phosphate adjuvant.

Robust cell mediated immune responses were also noted among CMV seronegative participants but no differences across dose groups of V160 were observed. Overall, cell mediated immune responses at all doses, and NAb responses at some doses (including 100U+ aluminum phosphate adjuvant) in CMV seronegative participants approximated those observed in naturally infected CMV seropositive participants.

All tested V160 formulations were safe and generally well-tolerated. No SAEs and no events of clinical interest (ECIs) (overdoses, pre-defined elevated hepatic enzyme, and autoimmune conditions) were reported. Overall, adjuvant-containing formulations were more reactogenic than unadjuvanted irrespective of dose. Across the different vaccination groups, the majority of AEs were the solicited injection site AEs (pain/tenderness, erythema/redness, and swelling) and the solicited systemic AEs (headache, fatigue, muscle pain, and joint pain); all of these events were transient and most were mild to moderate in intensity. No vaccine strain CMV was detected by polymerase chain reaction (PCR) in the saliva or urine of vaccine recipients.

Refer to the IB for further details regarding viral replication, virological characteristics of the vaccine virus, as well as detailed background information on animal studies.

Phase 2 Clinical Study (Ongoing)

A global Phase 2b study (V160-002) is currently being conducted to further evaluate the V160 formulation containing 100 units/dose + aluminum phosphate adjuvant, which elicited high CMV-specific NAb in study V160-001. Both humoral and cellular immune responses as well as protection against CMVi in CMV seronegative vaccine recipients are being assessed.

The study population in study V160-002 is women of child-bearing age and thus, healthy females between 16 and 35 years of age are included in the study. Infant outcomes of any study participant who becomes pregnant will be assessed to evaluate protection against cCMVi as well.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from intervention during participation, as clinical studies are designed to provide information about the safety and immunogenicity of an investigational vaccine.

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IB and Informed Consent Form (ICF) documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

There are no hypotheses for the study.

The following objectives will be evaluated in healthy Japanese male participants 20 years to 64 years of age inclusive.

Objectives	Endpoints
Primary	
To assess the safety and tolerability of a 3-dose regimen of V160 administered intramuscular (IM) by cytomegalovirus (CMV) serostatus.	• Solicited injection site adverse events (AEs) within Days 1 through 5 after each vaccination visit, and solicited systemic AEs, and vaccine-related serious adverse events (SAEs) within Days 1 through 14 after each vaccination visit
Secondary	
To evaluate CMV-specific neutralizing antibody (NAb) geometric mean titers (GMTs) at 1 month postdose (PD)3 in initially CMV-seronegative participants vaccinated with a 3-dose regimen of V160 administered IM.	• CMV-specific NAb titers
To evaluate viral detection, viral shedding, and viral leakage of V160 by the number and proportion of the participants with positive viral detection in plasma up to 14 days PD1, in urine and saliva up to 1 month PD3, and in injection-site swab and adhesive tape swab up to 30 minutes PD1 by CMV serostatus.	• Viral detection of V160 in plasma, urine and saliva, and injection-site swab and adhesive tape swab
Exploratory	
To evaluate seroconversion rate based on the NAb titers at 1 month PD3 in initially CMV-seronegative participants vaccinated with a 3-dose regimen of V160 administered IM.	• Seropositivity based on the NAb titers
To evaluate NAb GMT and geometric mean of CMV-specific NAb fold-rise (GMFR) at 1 month PD3 relative to Day 1 in initially CMV-seropositive participants vaccinated with a 3-dose regimen of V160 administered IM.	• CMV-specific NAb titers

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1, randomized, placebo-controlled, parallel-group, single-site, double-blinded, safety and immunogenicity study of V160 in healthy Japanese men 20 years to 64 years of age inclusive.

This study will evaluate the safety and immunogenicity of 3-dose regimen of V160 administered IM over 6 months in CMV-seropositive and CMV-seronegative of healthy Japanese men.

In this study, approximately 18 Japanese healthy male participants will be randomized in a 2:1 ratio with stratification by CMV serostatus (seropositive vs seronegative) to receive 3 IM injections of either 100 units/dose of V160 adjuvanted with aluminum phosphate adjuvant or placebo (saline solution) administered on Day 1, Month 2, and Month 6.

Participants will be considered to have completed the study if they received all 3 doses of study vaccine at the time points specified in the SoA and have completed the Month 7 study visit.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The primary objective of the study is to assess the safety and tolerability profiles of a 3-dose regimen of V160 administered IM in Japanese male participants 20 years to 64 years of age inclusive who are in good medical health at the start of the study. The selected population for this first study in Japanese participants is consistent with the population typically used in Phase I clinical studies, namely healthy adult male at low risk for disease, prior to include Japanese women of childbearing age in near future study. Considering possibility of future use in CMV seropositive population, this study will enroll CMV seropositive participants to collect safety and immunogenicity data as well as CMV seronegative ones. Approximately 18 participants will be enrolled in this study to include 9 CMV-seropositive and 9 CMV-seronegative individuals.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The purpose of the CMV-specific NAb assay is to assess humoral immunity by quantifying NAb titers to CMV before and after vaccination. This assay provided the primary serological readout in study V160-001, allows quantitative comparison of responses to different doses, and provides a functional characterization of the vaccine response. Also, seropositivity based on the Nab assay in initially CMV-seronegative participants will be assessed that is defined as NAb titer ≥assay defined cutoff level.

4.2.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the product's safety profile demonstrated in study V160-001.

In this study, as in study V160-001, solicited injection site AEs will be collected Days 1 to 5 following each dose of V160/placebo, and oral temperatures and pre-specified solicited systemic AEs including tiredness (fatigue), muscle pain (myalgia), headache, and joint pain (arthralgia) will be collected Days 1 to 14 following each dose of V160/placebo. SAEs will be collected for the duration of the participant's study participation (up to Month 7/Visit 8). The vaccine is conditionally replication defective and the vaccine virus will not replicate in the human body because Shield-1 is not present, regardless, specific safety measurements are being collected as outlined in Section 8.4.

The time points chosen for safety assessment are based on peak occurrence of AEs generally observed following vaccination in clinical studies with multi-dose vaccines. The investigator (or medically-qualified designee) will assess the vaccine relatedness of all serious and non-serious AEs, the intensity of all serious and non-serious AEs. During the Vaccination Report Card (VRC)-specified safety follow-up period (Day 1 through Day 14), clinical AEs will be recorded on a VRC by the participant on the day of occurrence. The investigator will use the information provided by the participant both on the VRC, and verbally at the time of VRC review.

Details on AEs, including definitions and reporting requirements, can be found in Appendix 3.

In addition, samples of saliva, urine, injection-site swab and adhesive tape swab will be collected at pre-specified times according to the SoA to evaluate the possible shedding, and leakage from the injection-site using a sensitive PCR assay. Furthermore, samples of blood (plasma) will be collected at pre-specified times up to Day 14 (SoA) as well to evaluate the possible biodistribution of vaccine virus in plasma using PCR assay.

4.2.1.3 Future Biomedical Research

The Sponsor will conduct future biomedical research on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

There is no commercially available CMV vaccine to serve as a comparator. A concurrent placebo control (sterile saline) is included in this study in order to compare safety profile and immunogenicity with those V160.

4.2.3 Rationale for Adjuvant

The aluminum phosphate adjuvant was assessed in study V160-001 where formulations containing aluminum phosphate adjuvant tended to be more immunogenic than those without, particularly at the 100 unit dose. Therefore, aluminum phosphate adjuvant is included in the V160 formulation for this Japan Phase 1 study. The dose level of aluminum phosphate adjuvant in the V160 formulation to be used in this study is consistent with the amount of aluminum phosphate adjuvant (125 µg/dose to 500 µg/dose) used in many other licensed vaccines.

4.3 Justification for Dose

The V160 formulation selected for this study is 100 Units/0.5 mL dose +225 µg of aluminum phosphate adjuvant as this formulation provided a safe and generally well tolerated profile with the greatest immunogenicity (measured by the NAb response) compared to the other dose groups in study V160-001. All participants randomized to the vaccine group will be given 3 injections of the V160 100 units/0.5 mL + aluminum phosphate adjuvant. The maximum dose at each dosing time point is the same as the minimum dose.

4.3.1 Rationale for Dose Interval and Study Design

The proposed dosing interval is intended to provide early induction of CMV-specific immune responses (with a second dose given within 2 months) and establishment of long term immunogenicity by providing a third dose at a later time (6 months). A 3-dose schedule of V160 administered at Day 1, Month 1, and Month 6 was used for study V160-001. For this Japan Phase 1 study, a Day 1, Month 2, and Month 6 schedule was selected to be consistent with the 3-dose regimen in the ongoing Phase 2b, proof of concept study in women of child-bearing age (V160-002). In Phase 2b, 2-dose regimen (Day 1, Month 6) will also be evaluated because it would allow greater compliance. Based on the results of Phase 2b, 2-dose or 3-dose regimen will be selected for Phase 3 studies.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last assay result.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy Japanese male participants between the ages of 20 and 64 (inclusive) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

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

1. Participant is healthy, based on medical history and physical examination.

2. Participant is serologically confirmed with CMV IgG as either CMV seropositive or CMV seronegative at Visit 1. Subjects who are indeterminate for CMV serostatus at randomization will be excluded from the study.

Demographics

3. Participant is Japanese Male.

4. Participant is from 20 years to 64 years of age inclusive, at the time of signing the informed consent.

Male Participants

5. A male participant are eligible to participate if they agree to the following from randomization through at least 4 weeks after the last dose of V160/placebo (from Day 1 through Month 7):

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

      OR

    - Must agree to use contraception unless confirmed to be azoospermic (Vasectomized or secondary to medical cause) as detailed below:
        - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) [Appendix 5] who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Informed Consent

6. The participant provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Protocol Adherence

7. The participant is able to read, understand, and complete study questionnaires (ie, the VRC).
8. The participant is able to complete all scheduled visits and to comply with the study procedures.
9. The participant agrees to provide study personnel with a primary telephone number as well as an alternate form of contact (eg, other telephone number, mailing address), if available, for follow-up purposes.

5.2 Exclusion Criteria

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

For items with an asterisk (*), if the subject meets these but not other exclusion criteria, the Day 1 Visit may be rescheduled for a time when these criteria are not met.

Medical Conditions

1. The participant has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with participation for the full duration of the study, as assessed by the investigator.

2. The participant has a history of any allergic reaction or an anaphylactic/anaphylactoid reaction to any vaccination that required medical intervention, or of any severe allergic reaction (eg, swelling of the mouth and throat, difficulty breathing, hypotension, or shock), to any vaccine component that required medical intervention.

3. *The participant has a recent (<72 hours prior to receipt of V160/placebo) history of febrile illness (temperature ≥38ºC, oral or equivalent).

4. The participant is planning donation of sperm at any time from signing the informed consent through 1 month after receiving the last dose of V160/placebo.

5. The participant is currently immunocompromised or has been diagnosed as having a congenital or acquired immunodeficiency, human immunodeficiency virus (HIV) infection, lymphoma, or leukemia. The participant with autoimmune conditions that require immunosuppressive medications (eg, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease) is also to be excluded. No testing for HIV will be required in the study.

6. The participant has a condition in which repeated venipuncture or injections pose more than minimal risk for the subject, such as hemophilia, thrombocytopenia, other severe coagulation disorders, or significantly impaired venous access.

7. The participant has major psychiatric illness including: any history of schizophrenia or severe psychosis, bipolar disorder requiring therapy, or any subject with suicidal ideation within 3 years.

Prior/Concomitant Therapy

8. The participant has previously received any CMV vaccine.

9. *The participant had any live virus vaccine administered or scheduled to be administered in the period from 4 weeks prior to, and 4 weeks following receipt of V160/placebo.

10. *The participant had any inactivated vaccine administered or scheduled within the period from 14 days prior to, through 14 days following V160/placebo.

11. The participant had administration of any immune globulin or blood product within 90 days prior to injection with V160/placebo or scheduled within 30 days thereafter.

12. The participant has received systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg) for ≥14 consecutive days and has not completed treatment at least 30 days prior to study entry.

13. The participant has received systemic corticosteroids exceeding physiologic replacement doses (≈5 mg/d prednisone equivalent) within 14 days prior to the first vaccination (participants using inhaled, nasal, or topical steroids are considered eligible for the study).

14. *The participant has received any anti-viral agent with proven or potential activity against CMV 14 days prior to vaccination or is likely to receive such an agent within 14 days after vaccination. Anti-viral agents prohibited include letermovir, ganciclovir, valganciclovir, foscarnet, and valacyclovir.

15. *The participant is receiving or has received in the year prior to enrollment immunosuppressive therapies including but not limited to rapamycin (also sirolimus), tacrolimus (also FK-506), or other therapies used for solid organ/cell transplant, radiation therapy, immunosuppressive/cytotoxic immunotherapy, chemotherapy and other immunosuppressive therapies known to interfere with the immune response. Topical tacrolimus is allowed provided that it is not used within 14 days prior to, or 14 days following V160/placebo.

Prior/Concurrent Clinical Study Experience

16. *The participant has participated in another clinical study in the past 4 weeks, or plans to participate in a treatment-based study or a study in which an invasive procedure is to be performed while enrolled in this study. (Participation in a safety surveillance or non-interventional study is acceptable).

Other Exclusions

17. The participant has a recent history (within the past 5 years) or current evidence of drug or alcohol abuse.

18. The participant is legally or mentally incapacitated.

19. Participant meets all eligibility criteria however, the number of participants required for enrollment based on CMV serostatus has been met.

20. Any other reason that in the opinion of the investigator might interfere with the evaluation required by the study.

21. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.2.1 Participant Deferment Criteria before Vaccination

These deferment criteria must be reviewed for each participant before each of second and third vaccination to ensure that none of the criteria apply to the participant and or that vaccination is deferred for an appropriate period of time. The participant would only be permitted to continue with a delayed vaccination if the vaccine can be administered within the allowed window. The participant should be deferred if:

1. Has a recent (<72 hours prior to receipt of V160/placebo) history of febrile illness (temperature ≥38.0°C, oral or equivalent).

2. Had any live virus vaccine administered or scheduled to be administered in the period from 4 weeks prior to, through 4 weeks following receipt of V160/placebo.

3. Had any inactivated vaccine administered or scheduled within the period from 14 days prior to, through 14 days following V160/placebo.

4. Had administration of any immune globulin or blood product within 90 days prior to injection with V160/placebo or scheduled within 30 days thereafter.

5. Had received systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg) for ≥14 consecutive days and has not completed treatment at least 30 days prior to any dose of study vaccination.

6. Had received systemic corticosteroids exceeding physiologic replacement doses (≈5 mg/d prednisone equivalent) within 14 days prior to any dose of study vaccination (use of inhaled, nasal, or topical steroids is allowed for the study).

7. Had administration of any anti-viral agent with proven or potential activity against CMV within 14 days prior to injection with V160/placebo or scheduled within 14 days thereafter. Anti-viral agents prohibited include letermovir, ganciclovir, valganciclovir, foscarnet, and valacyclovir.

8. Had administration of topical tacrolimus within 14 days prior to injection with V160/placebo or scheduled within 14 days thereafter.

5.2.2 Criteria to be Checked for Excluding Participants from Receiving Subsequent Doses

Specific exclusion criteria must be reviewed for each participant before administration of any subsequent dose of V160/placebo to ensure that none of the criteria apply to the participant. If any apply, the participant will be excluded from receiving the scheduled vaccination (and therefore be excluded from the per protocol analysis) but will continue in the study for all other follow-up procedures. A complete list of criteria to be checked prior to Dose 2 and Dose 3 are provided in Section 7.1.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study vaccination or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Inter-vention Group Name	Arm Type	Inter-vention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Administration	Vaccination Regimen	Use	IMP/NIMP	Sourcing
V160	Experi-mental	V160	Biological/ Vaccine	Lyophilized Cake (vial)	200 Units/mL	100 Units with 225 µg aluminum per 0.5 mL dose	IM	Day 1, Month 2, Month 6	Experi-mental	IMP	Sponsor
		APA Diluent	Other	Sterile Suspension (Vial) for reconstitution	450 µg/mL				Adjuvant	IMP	Sponsor
Placebo	Placebo Comparator	Sterile Saline Placebo	Other	Sterile Solution(vial)	Not applicable	0.5 mL	IM	Day 1, Month 2, Month 6	Placebo	IMP	Sponsor

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

Abbreviations: APA Diluent = Aluminum Phosphate Adjuvant (APA) Diluent, Sterile Saline Placebo = V160 Sterile Saline Placebo, Unit Dose Strength = Strength of the V160 and APA product after reconstitution, Dosage level = post reconstitution per 0.5 mL dose, IM = Intramuscular, IMP = Investigational Medicinal Product, NIMP = Non-Investigational Medicinal Product

All supplies indicated in Table 1 will be provided per the “Sourcing” row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

V160 (after reconstitution) and placebo will be prepared and administered in a blinded fashion by an unblinded qualified study site personnel because the two products are visually different (the vaccine is opaque and the placebo is clear). Unblinded personnel will be responsible for reconstitution of study vaccine in order to produce the final study vaccine formulation that will be administered to the participant. Blinded personnel will not be present during vaccine preparation and administration.

Reconstitution of V160 Lyophilized Cake:

Reconstitution of the V160 lyophilized cake should be completed within 90 minutes after removal from the refrigerated storage unit.

1. Remove V160 and aluminum phosphate adjuvant diluent vials from the refrigerated storage unit.

2. Mix the contents of the aluminum phosphate adjuvant diluent vial by shaking thoroughly to get a homogeneous mixture.

3. Using a syringe and needle, withdraw 0.7 mL of aluminum phosphate adjuvant diluent from the diluent vial, and inject immediately into the V160 lyophilized cake vial.

4. Gently swirl the V160 vial and examine for undissolved material. Continue swirling until the lyophilized cake has completely dissolved and the appearance is opalescent. Disregard any bubbles that may be present.

5. Withdraw and administer 0.5 mL of the reconstituted V160 vial.

Study vaccine should be administered immediately following dose preparation. If the reconstituted product is not used immediately, the vial/syringe contents should be mixed by inverting several times to get a homogeneous mixture of the product immediately prior to use. If the study vaccine or placebo is not administered within 60 minutes, it should be disposed of as a biohazardous medical waste and a new study vaccine should be prepared.

Preparation of Placebo:

The sterile saline placebo will be used as supplied.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to V160 group and placebo group, respectively.

6.3.2 Stratification

Intervention allocation/randomization will be stratified to 1:1 according to the CMV serostatus (seropositive : seronegative).

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. V160 (after reconstitution) and placebo will be prepared and administered in a blinded fashion by an unblinded qualified study site personnel because the two products are visually different (the vaccine is opaque and the placebo is clear). The participant, the investigator, and Sponsor personnel or

delegate(s) who are involved in the clinical evaluation of the participants are unaware of the intervention assignments.

In order to avoid bias, the unblinded individual/s will not be involved in any postdose safety assessment procedures. The unblinded individual/s also must not disclose any information regarding the allocation of the clinical supplies or the appearance of the V160/placebo to any blinded member of the site staff or to the participant. No blinded member of the site staff should have contact with the clinical supplies at any point during the course of the study.

Note that participants must be discontinued from vaccination if they become unblinded (Section 7.1).

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Study Intervention Compliance

Study compliance is defined in this study as participants who received all 3 doses of scheduled study vaccinations/placebo.

Interruptions from the protocol specified vaccination plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1 (Section 5.2) and prerequisites for other vaccination visits (Section 5.2.1).

Participants may receive allergen desensitization therapy and tuberculin skin testing while participating in the study.

Topical tacrolimus is allowed provided that it is not used 14 days prior to, or 14 days following a V160/placebo dose.

Use of prior and concomitant medications/vaccination should be recorded as described in Section 8.1.5.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

Dose modification is not allowed in this study.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the vaccination regimen will still continue to participate in the study as specified in Section 1.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's intervention assignment has been unblinded by the investigator, Sponsor, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant had an allergic reaction or an anaphylactic/anaphylactoid reaction that required medical intervention following Dose 1 or Dose 2 administration
- The participant enrolled in another interventional clinical study following Dose 1 or Dose 2 administration.
- The participant has received any prohibited medications or vaccinations since Dose 1 or Dose 2 administration (See Section 5.2.1 for prerequisites for the second and third vaccination visits).

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.1.9 for those procedures to be completed at each specified visit.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study,as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9.1. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 60.5 mL (Appendix 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research.If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study. An additional review of deferment/exclusion/discontinuation criteria will be done at the second and the third vaccination visits (Visit 6 and 7). These criteria are listed in Section 5.2.1, 5.2.2 and 7.1.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at the screening visit in order to ensure that the participant satisfies the inclusion and exclusion criteria of the study. The participant's medical conditions will be reported on the appropriate electronic case report form (eCRF), including any chronic or serious conditions.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication/vaccination use and record prior medication taken by the participant to assess inclusion and exclusion criteria including time windows for medication/vaccination use.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. As outlined in the exclusion criteria, there are specific restrictions for prior medications and vaccines, as well as concomitant medications and vaccines that are anticipated throughout the duration of the study. Investigators should make every attempt to adhere to the entry criteria concerning prior, concomitant, and anticipated medications and vaccines.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization.Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Note that participants who meet screening eligibility may be randomized outside of the 21-day window; however, all screening procedures must be repeated when a participant is not randomized within 21 days of Visit 1 (Screening). Participants who are re-screened must be randomized within 21 days of the re-screening visit.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

V160/placebo will be prepared and administered by an unblinded pharmacist/qualified study site personnel, who will do no further assessment of clinical outcomes in the participants. Open-label, single dose vials will be supplied to the unblinded individual/s at the clinical site. Supplies will be affixed with a clinical label in accordance with regulatory requirements, including the information as a genetically modified live vaccine.

Note that the V160/placebo should be administered within 60 minutes of preparation. Refer to Section 6.2.1 for details.

The V160/placebo will be administered intramuscularly in the deltoid muscle using the syringe by the unblinded physician. Injections of V160/placebo should be administered at a 90° angle into the muscle tissue using a needle long enough to ensure IM deposition of V160/placebo. A separate, sterile disposable unit should be used for the administration of V160/placebo to each participant. Needles should not be recapped. Safe disposal procedures should be handled in accordance with medical waste management regulations and infectious waste management regulations. Study participants will be observed for 30 minutes (for 3 hours on Visit 2 for another blood sampling) following each vaccination for any immediate AEs and longer if necessary. Adequate treatment provision, including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occurs.

Participants who meet any of the deferred exclusion criteria (criteria with asterisk in Section 5.2, and 5.2.1) should not be administered, and may subsequently return to the clinic to determine eligibility status prior to vaccination.

Prior to each subsequent vaccination, exclusion criteria for subsequent vaccination (Section 5.2.2 and Section 7.1) will be assessed.

8.1.8.1 Timing of Dose Administration

Dose 1 of study intervention for both V160 and placebo groups will begin on the day of intervention randomization at Visit 2 (Day 1). A second dose of study intervention will be given at Visit 6 (Month 2) and a third dose will be given at Visit 7 (Month 6).

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the 3-dose vaccination regimen should be encouraged to continue to be followed for all remaining study visits. Those procedures related to the following vaccination (i.e., to check postdose 1 exclusion criteria, vaccination, distribution of VRC, postdose observation) are not required for the participants at the following visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Visit 8/Month 7 visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Only the primary investigator or delegate and the respective participant's code should be unblinded. Other study site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

Once an emergency unblinding that is part of the study design has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose intervention assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.11 Distribution of Vaccination Report Card

The VRC was structured as recommended in the final FDA Patient Reported Outcome Guidance. The investigator or delegate will train the participant in the use of the VRC at Visit 2 (Day 1). Oral temperatures, injection site reactions, vaccine specific complaints, other complaints or illnesses and medications/vaccinations will be recorded on the VRC following each vaccination (refer to Section 8.3.3 for safety assessments using the VRC).

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Immunogenicity Assessments

Sera collected from all participants on Visit 2 (Day 1) and Visit 8 (Month 7) will be used to measure humoral immune responses to V160 using viral NAbs. Blood collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

8.2.1 Viral Neutralizing Antibody Assay

The viral NAb assay measures the functional antibodies blocking viral entry, and is considered the primary assay for immunogenicity. Note that all blood samples collected on the day of vaccination will be drawn prior to V160/placebo administration. Refer to Appendix 2 for additional details of the assay and volume of blood collected.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood and other samples to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/fluid volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 2.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations (Full and Targeted Examinations)

A full physical examination including vital signs (heart rate, respiratory rate, seated blood pressure, and oral temperature), height and weight will be conducted per institutional standard and recorded at the screening visit (Visit 1). Any clinically significant abnormality should be recorded on the appropriate eCRF. Special attention should be paid to clinical signs related to a previous serious illness.

A directed physical examination including vital signs should be performed prior to each vaccination and at the Month 7 visit.

8.3.2 Vital Signs and Body Temperature

- Heart rate, respiratory rate, blood pressure, and oral temperature will be assessed.

- Blood pressure and heart rate measurements will be assessed after the participant has at least 5 minutes of rest in a quiet setting without distractions, and from a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Oral temperatures will also be documented by participants using their VRC during the VRC-specified postvaccination follow-up period.

8.3.3 Safety Assessments Using the VRC

All participants will be observed for 30 minutes after each vaccination for any immediate reactions.If any immediate AEs are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event, must be recorded on the appropriate eCRF.

Participants will use the VRC (Section 8.1.11) to document the following information:

- Oral temperatures measured from Day 1 (day of vaccination) through Day 14 postdose; any temperature ≥38.0ºC oral or equivalent, will be considered an AE of fever.

- Solicited injection site AEs (pain/tenderness, erythema/redness, and swelling) from Day 1 through Day 5 postdose;

- Solicited systemic AEs (headache, tiredness, muscle pain, and joint pain) from Day 1 through Day 14 postdose;

- Any other injection-site or systemic AEs from Day 1 through Day 14 postdose; and

- Concomitant medications from Day 1 to Day 14 postdose.

In order to ensure that the VRC is being filled out without delay, telephone contacts to remind the subject will be conducted after 14 days from the second and the third vaccination, respectively.

The investigator or delegate will review the data captured on the VRC with the participant at the subsequent visit after each vaccination (refer to the SoA).

For AEs reported on the VRC, the investigator will use the information provided by the participant both on the VRC, and verbally at the time of VRC review, to apply the appropriate intensity grade as described in Appendix 3.

8.3.4 Clinical Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the operations/laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.4.1 CMV IgG Testing

For stratification, serum CMV IgG will be assessed by Enzyme immunoassay and the participant will be determined whether the serum is IgG (+) or IgG (-) at screening visit (Visit 1).

8.3.4.2 CMV PCR Testing

Plasma, swab from injection-site and adhesive tapes (inside and outside, respectively), urine and saliva will be collected from all participants at time points specified below and Appendix 2.

DNA will be extracted from each samples and assayed for the presence of CMV by a PCR assay. If CMV is detected, distinction between V160 vaccine virus and non-vaccine virus will be performed in a separate PCR assay, except swab samples.

Refer to Appendix 2 for a summary of the CMV PCR assay.

8.3.4.2.1 Plasma

Plasma samples will be collected at 3 points on Day 1 (prior to vaccination, 0-min and 3-hour post vaccination), and each 1 point on Day 3, 7, and 14 as shown in Appendix 2 in order to evaluate biodistribution of V160 in the human body. Blood will be drawn from the other arm from the vaccinated arm at the time point of just after vaccination on Day 1.

8.3.4.2.2 Swab

Swab samples will be collected at 4 points on Day 1 (0-min, 10-min, 20-min and 30-min post vaccination) from injection-site, and 3 points on Day 1 (10-min, 20-min and 30-min post vaccination) from adhesive tapes (inside and outside, respectively) as shown in Appendix 2, in order to evaluate viral leakage from injection-site to assess risk for horizontal infection of V160. Injection-site will be covered with an adhesive tape just after vaccination (after swab sampling from injection-site), and the adhesive tape will be changed by 10 minutes (after swab sampling from injection-site), ie, at 10 minutes and at 20 minutes after vaccination on Day 1. At 30 minutes after vaccination on Day 1, Month 2 and Month 6, the investigator or delegate should confirm that the injection-site of the participant is no longer bleeding prior to be free from covering with the adhesive tapes.

8.3.4.2.3 Urine and Saliva

Urine and saliva samples will be collected at each visit (7 points prior to vaccination from Day 1 through Month 7) specified in the SoA and Appendix 2 for evaluation of viral shedding.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of allocation/randomization through 14 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the participant completing the study, but outside the time period specified in the previous paragraph.

OR

2. An SAE that is considered by an investigator who is a qualified physician to be vaccine related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 2.

Table 2 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all from the time of each vaccination through 14 days thereafter.	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all for the duration of an individual's study participation.	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all for the duration of an individual's study participation.	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all for the duration of an individual's study participation.	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

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

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in

randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are males and partner pregnancy/lactation information is not required.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease related outcomes not qualifying as AEs or SAEs for this study.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor. There are no ECIs for this study.

8.5 Treatment of Overdose

In this study, an overdose is defined as receipt of more than 1 dose of study vaccine in a 24-hour period.

Sponsor does not recommend specific treatment for an overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- DNA for future research

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase I Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of V160 (Human Cytomegalovirus Vaccine) in Healthy Japanese Men
Intervention Assignment	Participants will be randomized in a 2:1 ratio to either V160 or Placebo, stratified by CMV serostatus.
Analysis Populations	Efficacy: Per Protocol Immunogenicity (PPI) population Safety: All participants as treated (APaT) population
Primary Endpoint	• Solicited injection site AEs within Days 1 through 5 after each vaccination visit • Solicited systemic AEs within Days 1 through 14 after each vaccination visit • Vaccine-related SAEs within Days 1 through 14 after each vaccination visit
Secondary Endpoint	• CMV-specific NAb titers at 1 month PD3 • Viral detection of V160 in plasma, urine and saliva, and injection-site swab and adhesive tape swab
Statistical Methods for Key Efficacy Analyses	CMV-specific NAb GMT at 1 month PD3 will be analyzed for seronegative participants using analysis of variance (ANOVA) model. The model will include term for intervention. The GMT ratio and 95% confidence intervals (CIs) will be estimated from this model.
Statistical Methods for Key Safety Analyses	Incidence of solicited injection site AEs, solicited systemic AEs and vaccine-related SAEs will be summarized for each serostatus, respectively.
Interim Analyses	No interim analyses are planned in this study.
Multiplicity	No multiplicity adjustment is planned in this study.
Sample Size and Power	A total of 9 participants will be enrolled for each CMV serostatus. Assuming a discontinuation rate of approximately 20%, 7 participants are expected to complete intervention.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the SPONSOR. This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

9.3 Hypotheses/Estimation

There are no hypotheses for the study. Objectives are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Immunogenicity Endpoints

Secondary Endpoint

- Geometric mean of CMV-specific NAb titers at 1 month PD3 in initially CMV-seronegative participants

Exploratory Endpoints

- Percent Seropositivity (Defined by NAb titer ≥assay defined cutoff level) at 1 month PD3 in initially CMV-seronegative participants
- Geometric mean of CMV-specific NAb titer at 1 month PD3 in initially CMV-seropositive participants
- Geometric mean of CMV-specific NAb fold-rise at 1 month PD3 relative to Day 1 (GMFR) in initially CMV-seropositive participants

9.4.2 Safety Endpoints

- Solicited injection site AEs within Days 1 through 5 after each vaccination visit, solicited systemic AEs and vaccine-related SAEs within Days 1 through 14 after each vaccination visit
- Viral detection of V160 in plasma, urine and saliva, and injection-site swab and adhesive tape swab

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

Per Protocol Immunogenicity (PPI) population
The PPI population will serve as primary immunogenicity analysis. To be eligible for inclusion in the PPI population, study participants must satisfy the following criteria:

- Participants have received all 3 vaccinations within the vaccination visit window specified in the SoA (Section 1.3).
- Have not deviated from protocol in ways that could affect the immune response to vaccination

The final determination of protocol deviations that could affect immune response to vaccination, and thereby the composition of the PPI population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

Participants will be included in the intervention group to which they are randomized for the analysis of immunogenicity. Details on the approach to handling missing data are provided in Section 9.6 Statistical Methods.

Full Analysis Set (FAS)
The FAS will serve as a supportive analysis population for Immunogenicity. The FAS population consists of all randomized participants who received at least 1 vaccination and have at least one post-randomization observation for the analysis endpoint.

9.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety in this study. The APaT population consists of all randomized participants who received at least one vaccination and defined according to the regimen of clinical material actually received (ie, received only vaccine, or received only placebo). Participants who received a mixture of vaccine and placebo are deemed ineligible for inclusion in the APaT population. Safety data of participants ineligible for inclusion in the APaT population will be summarized in listings.

9.6 Statistical Methods

9.6.1 Statistical Methods for Immunogenicity Analyses

CMV-specific NAb GMT at 1 month PD3 will be analyzed for seronegative participants using an ANOVA model. The NAb titers will be log-transformed prior to analysis. The model will include term for intervention. The treatment difference and corresponding 95% confidence interval (CI) will be estimated at 1 month PD3 on the log-transformed data. Estimates of treatment difference and corresponding 95% CI will then be back-transformed to get the GMT ratio and the 95% CI for GMT ratio. Methods related to exploratory endpoint will be described in sSAP.

Table 3 summarizes the analysis plans relating to the immunogenicity endpoints.

Table 3 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (1 month PD3)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Secondary				
CMV-specific NAb GMT at 1 month PD3	P	ANOVA	PPI (seronegative participants)	observed data
CMV-specific NAb GMT at 1 month PD3	S	ANOVA	FAS (seronegative participants)	observed data

† P=Primary approach, S=Supportive approach.

ANOVA: analysis of variance, PPI:Per Protocol Immunogenicity, FAS: Full Analysis Set

Handling of Missing Data

All analyses will be conducted based on the observed data only.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and vital signs. All participants who are vaccinated and eligible for inclusion in the APaT population as defined in Section 9.5.2 will be included in the safety analyses and summaries. Incidence of AEs will be summarized as frequencies and percentages by vaccination group.

To provide an overall assessment, safety measures such as the incidence of the following events occurring throughout the study will be summarized for each serostatus, respectively:

1) any AE,

2) any injection-site AE,

3) any systemic AE,

4) any SAE,

5) any vaccine-related SAE,

6) any discontinuation due to an AE within 14 days of receipt of any study vaccination

AEs will be summarized by vaccination visit and across all vaccination visits. Specific AEs for which summaries will be provided are identified in Table 4.

-The number and percent of the participants with positive viral shedding in urine and saliva up to 1 month postdose 3 (defined by viral load in saliva/urine ≥ assay defined threshold cutoff value) will be also summarized for generic CMV and for vaccine-type virus separately, by vaccination group by CMV serostatus.

-The number and percent of the participants with positive viral detection in plasma up to 14 days postdose 1 (defined by viral load in plasma ≥ assay defined threshold cutoff value) will be also summarized for generic CMV and for vaccine-type virus separately, by vaccination group by CMV serostatus.

-The number and percent of the participants with positive viral leakage in injection-site swab and adhesive tape swab up to 30 minutes postdose 1 (defined by viral load in injection-site swab/adhesive tape swab ≥ assay defined threshold cutoff value) will be also summarized for generic CMV by vaccination group by CMV serostatus.

-The oral temperatures recorded on the VRC will also be summarized.

Table 4 Safety Analyses of Adverse Events Endpoints

Adverse Events endpoints	Time Window		
	Day1 to Day 5†	Day 1 to Day 14†	Any Time during Study
-Solicited Injection site AEs of pain/tenderness, erythema/redness, and swelling	●		
-Unsolicited injection site AEs		●	
-Solicited systemic AEs of fatigue, myalgia, headache and arthralgia		●	
-Unsolicited systemic AEs		●	
-Serious AEs		●	
-VR SAEs		●	
- Discontinuation due to an AE		●	
-Elevated temperature§		●	
-Death			●
-Any AE		●	
-Saliva/Urine viral Shedding*			●
-Viral detection from plasma*			●
-Viral leakage from swab sampling of injection-site/adhesive tape*			●

Summaries will be provided by vaccination group separately for the participants in each serostatus.

† The day of vaccination is counted as Day1. Day 1 to Day 5 refers to the day of vaccination plus 4 days immediately post-vaccination. Day 1 to Day 14 refers to the day of vaccination plus 13 days immediately post-vaccination.

* The viral shedding, viral detection from plasma, and viral leakage data will be summarized as percentage of positivity by Visit; the duration for collecting viral shedding is shown in SoA.

§ Defined as ≥38.0ºC oral or equivalent.

AE=Adverse Events, SAE=Serious Adverse Events, VR=Vaccine-Related.

9.6.3 Demographic and Baseline Characteristics

The comparability of the vaccination groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by vaccination and serostatus either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

No multiplicity adjustment is planned for this study.

9.9 Sample Size and Power Calculations

Nine participants will be randomized in a ratio of 2:1 into V160 and placebo for each CMV serostatus cohort.

If a specific AE is not observed in any of the 6 participants in V160, then the true incidence of that event is 46% or less with 90% confidence.

9.10 Subgroup Analyses

No subgroup analyses are planned for this study.

9.11 Compliance (Medication Adherence)

Compliance to vaccination will be summarized by number and percent of subjects in each vaccination group who received vaccination dose 1, vaccination dose 2, and vaccination dose 3.

9.12 Extent of Exposure

The summary of the number and percent of subjects in the V160 group who received vaccination dose 1, vaccination dose 2, and vaccination dose 3 also serve as the summary of subjects who received 100 units, 200 units, and 300 units, respectively, of V160.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutiona Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

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

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarmen

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

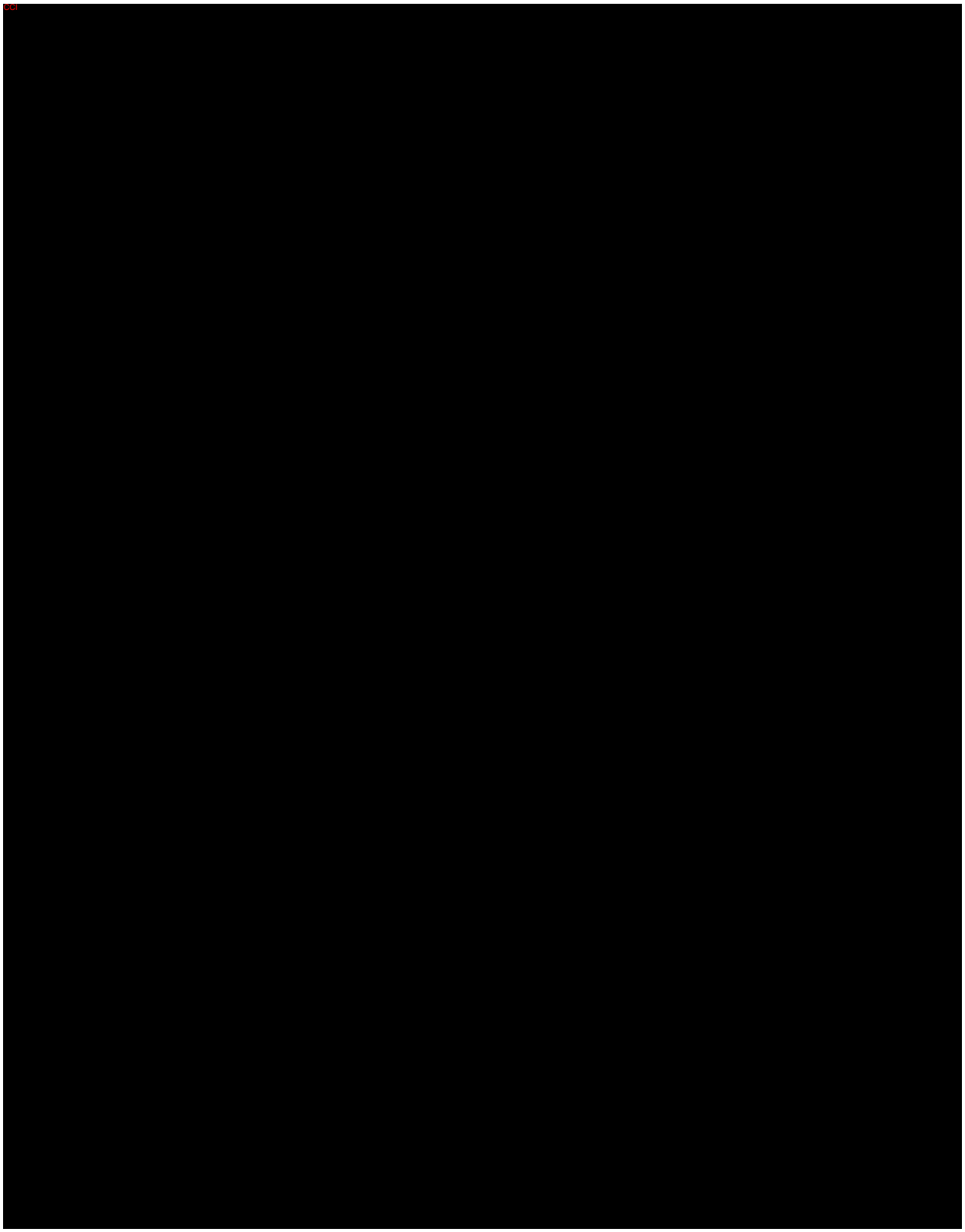
Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical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

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests



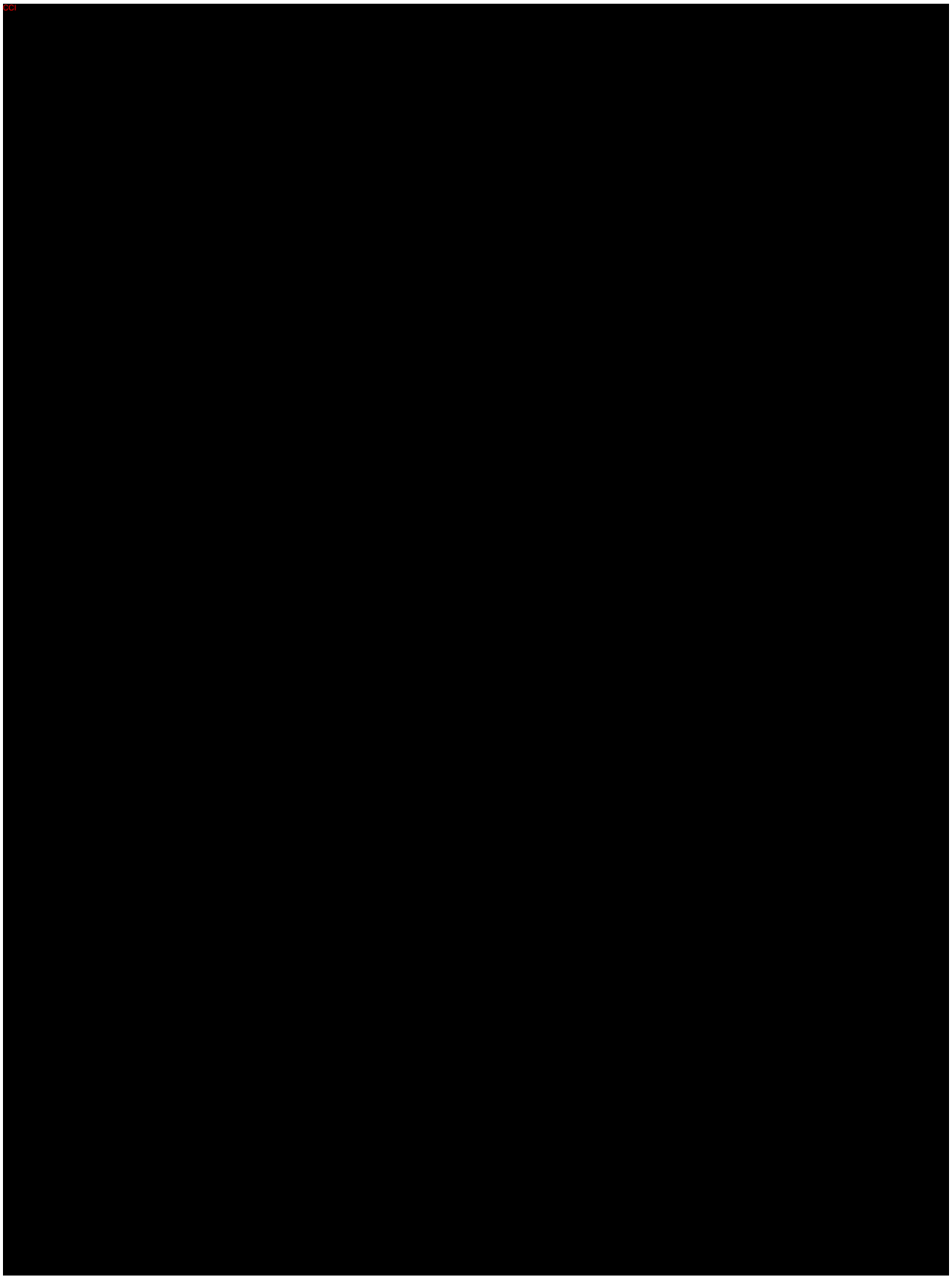


Table 5 Protocol-required Laboratory Assessments

Visit Number/Title		Visit 1 Screening	Visit 2/Day 1						Visit 3 Day 3	Visit 4 Day 7	Visit 5 Day 14	Visit 6 Month 2 (Day 60)	Visit 7 Month 6 (Day 180)	Visit 8 Month 7 (Day 210)	Approx. Blood Volume Collected
Assay	Sample		prior to vac	0 min after vac	10 min after vac	20 min after vac	30 min after vac	3 hour after vac							
Scheduling Window		-21 to -1 days	- 1 hr	+ 5min	+/- 5min	+/- 5min	+/- 5min	+/- 10min	+/- 1 day	+/- 2 days	+/- 2 days	+14 days	+14 days	+14 days	Not applicable
CMV IgG testing	Blood (Serum)	X													2.0 ml
Future Biomedical Research	Blood		X												8.5 ml
Neutralizing Antibody assay	Blood(Serum)		X											X	20 ml (10 ml/ time point)
CMV PCR assay	Blood (Plasma)		X	X				X	X	X	X				30 ml (5 ml/ time point)
	Swab from injection-site [1]			X	X	X	X								Not applicable
	Swab from adhesive tape (inside)[2]				X	X	X								Not applicable
	Swab from adhesive tape (outside) [2]				X	X	X								Not applicable
	Urine		X						X	X	X	X	X	X	Not applicable
	Saliva		X						X	X	X	X	X	X	Not applicable
														Total Blood Volume Collected	60.5 ml

CMV: cytomegalovirus, IgG: immunoglobulin G, PCR: polymerase chain reaction ,vac: vaccination

[1] Wipe the skin with an alcohol swab AFTER collection of the injection-site swab and the Band-Aid.

[2] Collect samples from inside and outside of 3 adhesive tapes covered over injection-site, changed by 10 min.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

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

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or 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 participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).
- Injection site erythema/redness or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
- No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study vaccination, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being

answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the Future Biomedical Research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

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3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ANOVA	analysis of variance
APaT	all participants as treated
BAC	bacterial artificial chromosome
cCMVd	congenital cytomegalovirus disease
cCMVi	congenital cytomegalovirus infection
CI	confidence interval
CMV	cytomegalovirus
CMVi	cytomegalovirus infection
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFP	green-fluorescent protein
GMFR	geometric mean fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
NAb	neutralizing antibody
PCR	polymerase chain reaction
PD	postdose
PK	pharmacokinetic
PPI	Per Protocol Immunogenicity
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RT-PCR	real time quantitative polymerase chain reaction
SAE	serious adverse event
SLAB	Supplemental Lab
SoA	schedule of activities
sSAP	supplemental statistical analysis plan

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
VRC	Vaccination Report Card
WOCBP	woman/women of childbearing potential

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