Official Protocol Title:	An Open-Label, Multicenter, Single-arm Study to Evaluate the Immunogenicity of VARIVAX™ in Healthy Russian Individuals 12 Months of Age and Older
NCT number:	NCT03843632
Document Date:	18 April 2019

Title Page

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Protocol Title: An Open-Label, Multicenter, Single-arm Study to Evaluate the Immunogenicity of VARIVAX™ in Healthy Russian Individuals 12 Months of Age and Older

Protocol Number: 058-05

Compound Number: V210

Sponsor Name:

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

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	0375
EudraCT	Not Applicable

Approval Date: 18 April 2019

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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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
V210-058-00	30-AUG-2012	Base protocol
V210-058-01	06-DEC-2012	The pregnancy/contraceptive follow-up period text was changed to be consistent with the Investigator Brochure and the Product Label.
V210-058-02	18-APR-2013	The study design was updated to include the enrollment targets by age groups and specified the primary immunogenicity and safety endpoints of the study. Laboratory tests were added for participants 7 years of age and older.

Document	Date of Issue	Overall Rationale
V210-058-03	Approved by the Document Review Committee on 20-APR-2015; however, the clinical study was put on hold before study start, by the Sponsor. Approved by Document Review Committee 2 on 07-JUN-2018, by the Late Stage Development Review Committee on 02-JUL-2018, and by the Protocol Review Committee on 17-JUL-2018. Resubmitted to the Russian Ministry of Health on 03-OCT-2018.	The title of the study was edited to remove "safety" and "tolerability", in order to align with the study's primary focus of immunogenicity, and secondary objective related to safety and tolerability. The study design was revised to include an adult cohort with a target enrollment of 50 participants. This cohort is referred to as Stage 1. Stage 2 would then enroll children and adolescents and follow sequentially after Stage 1. Additionally, the ages of children and adolescent participants in Stage 2 of the study were specified.
V210-058-04	18-DEC-2018	Added an exclusion criterion to exclude participants who have (or their parents have) a documented human immunodeficiency virus (HIV) infection, untreated syphilis infection or viral hepatitis infection (Hepatitis B or C).
V210-058-05	18-APR-2019	The protocol content was formatted to align with the current version of the Common Protocol Template (CPT).

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

The primary reason for Protocol Amendment 5 was to align it with the current version of the Common Protocol Template (CPT).

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Various sections	Protocol content formatted to align with current version of the Common Protocol Template. Sections have been reorganized and new content has been added to Sections 10.2 and 10.8.	Authoring template updated to align with the new version (V4.0) of the Common Protocol Template.
1.2 Schema	Revised study diagram to present the study design by stage.	To separate Stage 1 participants (adults) from Stage 2 participants (adolescents and children).

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Created separate SoAs for adolescents/adults and children. Added indication for temperature assessment prior to each vaccination. Added review of prior/concomitant medications and non-study vaccination to final study visit. Removed the collection of blood for complete blood count (CBC), chemistry, and the urinalysis sample at Visit 1 for participants <7 years of age.	To more clearly reflect the different assessments performed in adolescents/adults vs. children. To provide specificity for temperature measurement pre-vaccination. To correct an inadvertent omission. To correct an inadvertent/incorrect entry. The CBC, chemistry and, urinalysis tests are only performed for participants 7 years of age and older.
2.2 Background	Updated number participants exposed during clinical studies with VARIVAX™.	To reflect clinical study data accrued since the last amendment.
2.2 Background and 2.3 Benefit/Risk Assessment	Updated number of VARIVAX™ doses distributed worldwide.	To update the number of VARIVAX™ doses distributed worldwide as of 16-MAR-2018.
4.1 Overall Design and 5 Study Population	Clarified enrollment eligibility of participants with a negative clinical history for varicella and/or herpes zoster.	To accurately reflect enrollment by clinical history, rather than laboratory history (serological status).

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Added mention of baseline blood sample collection for the evaluation of varicella-zoster virus (VZV) antibody responses prior to vaccination.	For clarity and to align with the Schedule of Activities (SoA).
5.1 Inclusion Criteria (Inclusion Criterion 1)	Replaced "Be 12 months of age or older." with "Be 12 months to 75 years of age (inclusive), at the time of signing the informed consent/assent form."	For consistency with other sections of the protocol, which specify upper age limit eligible for enrollment at 75 years of age.
5.2 Exclusion Criteria	Revised exclusion criterion 6: to also exclude study participants who live with a person who has any congenital or acquired immune deficiency, neoplastic disease, or depressed immunity.	To address potential risk of vaccine-type viral transmission to at-risk immediate contacts.
8.4.7 Events of Clinical Interest (ECIs) and 8.5 Definition and Treatment of Overdose	Revised the reporting timeframe for ECIs to the Sponsor from "within 24 hours" to "within 5 calendar days".	To align with Patient Data Acquisition and Management - Next Generation requirements.
9.10 Subgroup Analyses	Added subgroup analyses for Stage 2 portion of the study.	To include analysis by age and dosing schedule for Stage 2 participants.

Section # and Name	Description of Change	Brief Rationale
Various sections	Minor editorial and document formatting revisions. Global terminology changes (eg, "subjects" to "participants", "trial" to "study", "violation" to "deviation", "adverse experience" to "adverse event", "parent/adoptive parent" to "participant's legally acceptable representative", "worksheets" to "case report forms/worksheets").	To improve the clarity of the document. Terminology changed in accordance with current Common Protocol Template.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Multicenter, Single-arm Study to Evaluate the Immunogenicity of VARIVAX™ in Healthy Russian Individuals 12 Months of Age and Older

Short Title: Evaluation of the Immunogenicity of VARIVAX™ in Healthy Russian Individuals

Acronym: V210-058

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in Russian individuals 12 months to 75 years of age with a negative clinical history of varicella and/or herpes zoster. No formal hypotheses will be tested in the study.

Primary Objectives	Primary Endpoints
Objective: To describe the immunogenicity of VARIVAX™ after: - Two doses of VARIVAX™, given 6 weeks apart, in adults 18 to 75 years of age (Stage 1). - Two doses of VARIVAX™, given 6 weeks apart, in adolescents 13 to 17 years of age (Stage 2). - One dose of VARIVAX™ in children 12 months to 12 years of age (Stage 2).	Participants who are seronegative at baseline (baseline VZV antibody titer <1.25 gpELISA units/mL): - Antibody response rate (percentage of participants with VZV antibody titer ≥5 gpELISA units/mL at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents/adults). - Geometric mean titers (GMTs) of VZV antibody as measured by gpELISA at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents/adults. - VZV seroconversion rate (percentage of participants with VZV antibody titer ≥1.25 gpELISA units/mL at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents/adults). Participants who are seropositive at baseline (baseline VZV antibody titer ≥1.25 gpELISA units/mL): - GMTs at Day 1 and 6 weeks postvaccination for children and at Day 1 and 6 weeks postdose 2 for adolescents/adults. - Geometric mean fold rise (GMFR) from Day 1 to 6 weeks postvaccination for children and from Day 1 to 6 weeks postdose 2 for adolescents/adults. - Percentage of participants with ≥4-fold rise in antibody titer from Day 1 to 6 weeks postvaccination for children and from Day 1 to 6 weeks postdose 2 for adolescents/adults.

Secondary Objectives	Secondary Endpoints
Objective: To summarize the safety and tolerability of VARIVAX™.	Following each vaccination with VARIVAX™: - Solicited injection-site reactions (redness, swelling, and pain/tenderness) of any intensity or size from Day 1 through Day 5 postvaccination. - Unsolicited injection-site adverse events from Day 1 through Day 42 postvaccination. - Maximum reported temperature ≥39.0°C oral equivalent from Day 1 through Day 28 postvaccination. - Varicella-, and herpes zoster-like rashes occurring from Day 1 through Day 42 postvaccination. - Systemic adverse events from Day 1 through Day 42 postvaccination. - Serious adverse events from Day 1 through Day 42 postvaccination. Vaccine-related serious adverse events and death from Day 1 through the end of the study period (42 days following the last vaccination) for each participant. A summary of blood and urine tests performed 3 days following each vaccination for participants 7 years of age and older.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Active immunization for the prevention of varicella in individuals 12 months of age and older
Population	Healthy individuals age 12 months to 75 years of age
Study Type	Interventional
Intervention Model	Single Arm This is a multi-site study.
Type of Control	No control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 24 months from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 150 participants will be allocated as described in Section 4.1.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Vaccine</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Vaccination Regimen</th><th>Use</th></tr>
<tr><td>Stage 1: Adults (18 to 75 years of age)</td><td>VARIVAX™</td><td>Refer to product labeling</td><td>2 doses</td><td>SC</td><td>2 doses given 6 weeks apart (Day 1 and Day 43 [+14])</td><td>Experimental</td></tr>
<tr><td>Stage 2: Adolescents (13 to 17 years of age)</td><td>VARIVAX™</td><td>Refer to product labeling</td><td>2 doses</td><td>SC</td><td>2 doses given 6 weeks apart (Day 1 and Day 43 [+14])</td><td>Experimental</td></tr>
<tr><td>Stage 2: Children (7 to 12 years of age)</td><td>VARIVAX™</td><td>Refer to product labeling</td><td>Single dose</td><td>SC</td><td>1 dose given on Day 1</td><td>Experimental</td></tr>
<tr><td>Stage 2: Children (12 months to 6 years of age)</td><td>VARIVAX™</td><td>Refer to product labeling</td><td>Single dose</td><td>SC</td><td>1 dose given on Day 1</td><td>Experimental</td></tr>
<tr><td colspan="7">Abbreviations: Admin. = administration; SC = subcutaneous</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>4 intervention groups: Stage 1 (adults 18 to 75 years), Stage 2 (adolescents 13 to 17 years), Stage 2 (children 7 to 12 years), and Stage 2 (children 12 months to 6 years)</td></tr>
<tr><td>Duration of Participation</td><td>Each participant who is 13 to 75 years of age (inclusive) will participate in the study for approximately 4 months, from the time the informed consent/assent form is signed through the final contact.

Each participant who is 12 months to 12 years of age (inclusive) will participate in the study for approximately 2 months, from the time the informed consent/assent form is signed through the final contact.</td></tr>
</table>

Study Governance Committees:

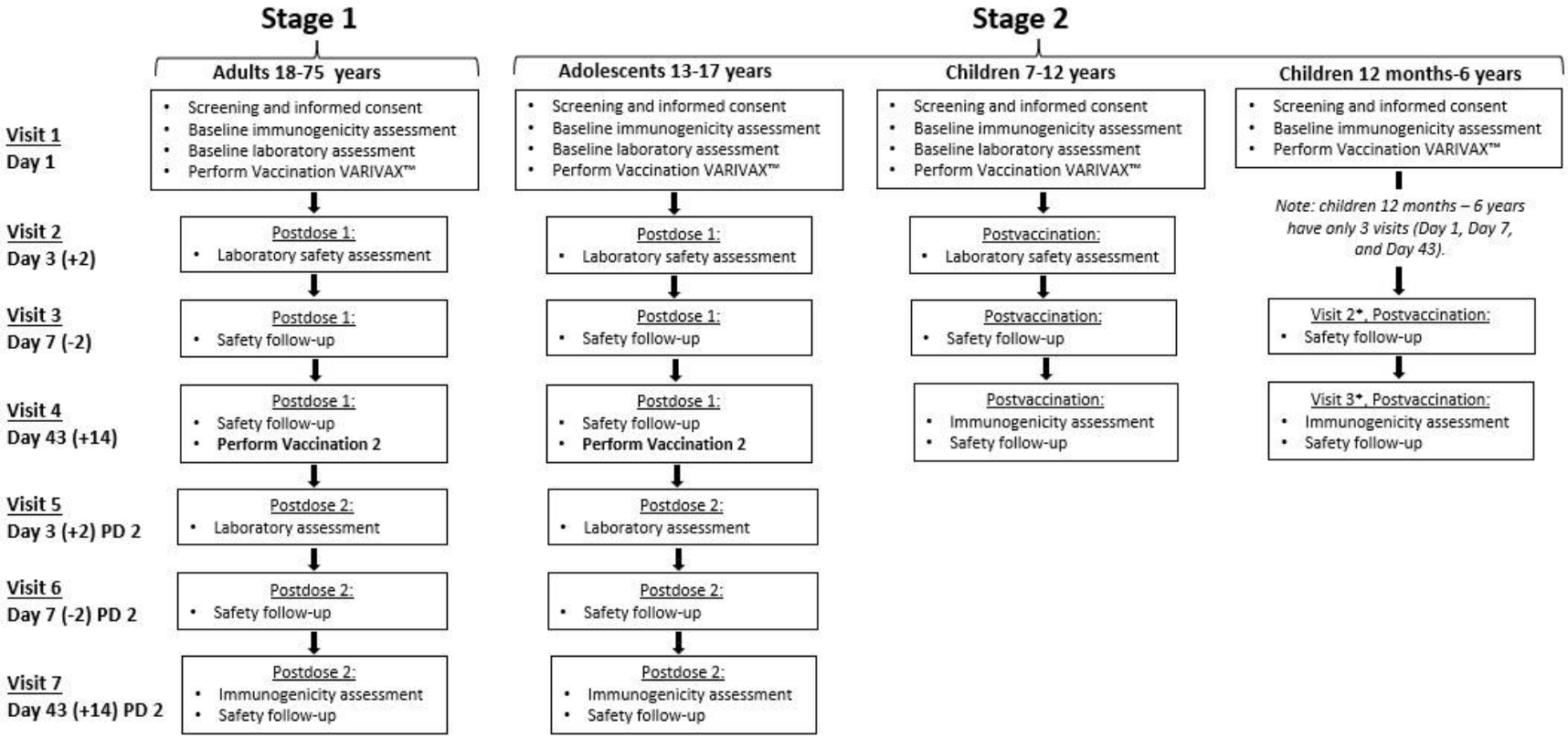
Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
Study governance considerations are outlined in Appendix 1.	

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.



*Visits 2 and 3 for children 12 months to 6 years of age occur at the same time as Visits 3 and 4, respectively, for participants 7 years of age and older.

Figure 1 V210-058 Study Design

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities (SoA) for Adults 18-75 Years (Stage 1) and Adolescents 13-17 Years (Stage 2)

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	Notes
	Dose 1	**Postdose 1**		**Dose 2**	**Postdose 2**			
Scheduled Day:	**Day 1**	**Day 3 PD 1**	**Day 7 PD 1**	**Day 43 PD 1**	**Day 46 PD 1 Day 3 PD 2**	**Day 50 PD 1 Day 7 PD 2**	**Day 86 PD 1 Day 43 PD 2**	
Visit Window:	**n/a**	**(+2 days)**	**(-2 days)**	**(+14 days)**	**(+2 days)**	**(-2 days)**	**(+14 days)**	
Administrative and General Procedures								
Informed Consent	X							Consent must be obtained before any study procedures.
Informed Consent for FBR	X							Must be obtained before the collection of buccal swab DNA samples.
Assignment of Screening Number	X							
Inclusion/Exclusion Criteria	X							
Participant Identification Card	X							
Temperature Assessment	X			X				Should be performed prevaccination.
Medical History	X							
Prior/Concomitant Medication and Non-Study Vaccination Review	X			X			X	
Assignment of Treatment Number	X							

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	Notes
	Dose 1	**Postdose 1**		**Dose 2**	**Postdose 2**			
Scheduled Day:	**Day 1**	**Day 3 PD 1**	**Day 7 PD 1**	**Day 43 PD 1**	**Day 46 PD 1 Day 3 PD 2**	**Day 50 PD 1 Day 7 PD 2**	**Day 86 PD 1 Day 43 PD 2**	
Visit Window:	**n/a**	**(+2 days)**	**(-2 days)**	**(+14 days)**	**(+2 days)**	**(-2 days)**	**(+14 days)**	
VARIVAX™ Administration	X			X				Review all eligibility criteria prior to vaccination.
Distribute Vaccination Report Card (VRC)	X			X				Use ruler and thermometer provided.
Educate Participants on the Definition and Reporting of SAEs	X							
Immunogenicity Procedures								
Blood Sample for Immunogenicity Testing	X						X	Blood samples must be collected before vaccination.
Safety Procedures								
Pregnancy Test (WOCBP only)	X			X				Performed by site/local laboratory. Must have negative results prior to vaccination.
Blood for CBC and Chemistry	X	X			X			Visits 2 and 3 may be combined. Visits 5 and 6 may be combined.

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	Notes
	Dose 1	**Postdose 1**		**Dose 2**	**Postdose 2**			
Scheduled Day:	**Day 1**	**Day 3 PD 1**	**Day 7 PD 1**	**Day 43 PD 1**	**Day 46 PD 1 Day 3 PD 2**	**Day 50 PD 1 Day 7 PD 2**	**Day 86 PD 1 Day 43 PD 2**	
Visit Window:	**n/a**	**(+2 days)**	**(-2 days)**	**(+14 days)**	**(+2 days)**	**(-2 days)**	**(+14 days)**	
Urinalysis Sample	X	X			X			Visits 2 and 3 may be combined. Visits 5 and 6 may be combined.
30-Minute Postvaccination Observation Period	X			X				
Review VRC			X	X		X	X	Includes varicella- and herpes-like rashes reporting. Refer to Section 8.3.1.
Review AEs and SAEs			X	X		X	X	

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	Notes
	Dose 1	**Postdose 1**		**Dose 2**	**Postdose 2**			
Scheduled Day:	**Day 1**	**Day 3 PD 1**	**Day 7 PD 1**	**Day 43 PD 1**	**Day 46 PD 1 Day 3 PD 2**	**Day 50 PD 1 Day 7 PD 2**	**Day 86 PD 1 Day 43 PD 2**	
Visit Window:	**n/a**	**(+2 days)**	**(-2 days)**	**(+14 days)**	**(+2 days)**	**(-2 days)**	**(+14 days)**	
Future Biomedical Research								
Buccal Swab Samples for FBR	X							Should be collected prior to vaccination, on Day 1, from enrolled participants who provide FBR consent only, or at a later date as soon as the informed consent is obtained.

AE = adverse event; CBC = complete blood count; DNA = deoxyribonucleic acid; FBR = future biomedical research; PD = postdose; SAE = serious adverse event; VRC = Vaccination Report Card; WOCBP = women of childbearing potential

1.3.2 Schedule of Activities (SoA) for Children 12 Months to 12 Years of Age

Visit Number	**1**	**2**	**3**	**4**	Notes
	Vaccination	**Postvaccination**			
Scheduled Day and Window:	**Day 1**	**Day 3 (+2 days)**	**Day 7 (-2 days)**	**Day 43 (+14 days)**	
Administrative and General Procedures					
Informed Consent	X				Consent must be obtained before any study procedures.
Informed Consent for FBR	X				Must be obtained before the collection of buccal swab DNA samples.
Assignment of Screening Number	X				
Inclusion/Exclusion Criteria	X				
Participant Identification Card	X				
Temperature Assessment	X				Should be performed prevaccination
Medical History	X				
Prior/Concomitant Medication Review	X			X	
Assignment of Treatment Number	X				
VARIVAX™ Administration	X				Review all eligibility criteria prior to vaccination.
Distribute Vaccination Report Card (VRC)	X				Use ruler and thermometer provided.
Educate Participants on the Definition and Reporting of SAEs	X				
Immunogenicity Procedures					
Blood Sample for Immunogenicity Testing	X			X	Blood samples must be collected before vaccination.

Visit Number	**1**	**2**	**3**	**4**	Notes
	Vaccination	**Postvaccination**			
Scheduled Day and Window:	**Day 1**	**Day 3 (+2 days)**	**Day 7 (-2 days)**	**Day 43 (+14 days)**	
Administrative and General Procedures					
Safety Procedures					
Blood for CBC and Chemistry	X	X			Participants 7 years of age and older ONLY. Visits 2 and 3 may be combined.
Urinalysis Sample	X	X			Participants 7 years of age and older ONLY. Visits 2 and 3 may be combined.
Postvaccination Observation Period	X				Observe children <3 years of age for at least 60 minutes; children ≥3 years of age for at least 30 minutes.
Review VRC			X	X	Includes varicella- and herpes-like rashes reporting. Refer to Section 8.3.1
Review AEs and SAEs			X	X	
Future Biomedical Research					
Buccal Swab Samples for FBR Research	X				Should be collected prior to vaccination, on Day 1, from enrolled participants who provide FBR consent only, or at a later date as soon as the informed consent is obtained.

AE = adverse event; CBC = complete blood count; DNA = deoxyribonucleic acid; FBR = future biomedical research; SAE = serious adverse event; VRC = Vaccination Report Card.

2 INTRODUCTION

VARIVAX™ is a live-attenuated vaccine indicated for the prevention of varicella in individuals 12 months of age and older.

2.1 Study Rationale

VARIVAX™ is not currently licensed in Russia. This is an open-label, multicenter, single-arm bridging study to evaluate the immunogenicity of VARIVAX™ in healthy Russian individuals. The study will enroll eligible individuals, 12 months through 75 years of age, which represents the age range for which a license is sought.

2.2 Background

The long-standing VARIVAX™ clinical development program has demonstrated VARIVAX™ to be highly immunogenic in healthy children, adolescents, and adults within 6 weeks after the recommended number of injections (1 injection for healthy children and 2 injections 4 to 8 weeks apart for healthy adolescents and adults). An optional 2-dose regimen of VARIVAX™ in children 12 months to 12 years of age induces higher varicella-zoster virus (VZV) antibody responses postvaccination compared with a 1-dose regimen, as measured by the percentage of participants with VZV antibody titers ≥5 glycoprotein antigen-based enzyme-linked immunosorbent assay (gpELISA) units/mL and geometric mean titers (GMTs). A second dose of VARIVAX™ induces a strong VZV antibody response, whether given 3 months or 3 to 6 years after the first dose. VZV antibodies persist in a very high proportion of healthy children, adults, and adolescents for at least 10 years after vaccination with the recommended number of injections (1 or 2 injections for healthy children and 2 injections 4 to 8 weeks apart for healthy adolescents and adults).

Long-term follow-up of vaccinees for up to 15 years has shown that low varicella breakthrough rates are maintained, suggesting that the protection afforded by the vaccine is durable [Ray, P., et al 2010][Saddier, P., et al 2009]. Epidemiologic studies in the US and other countries, conducted since VARIVAX™ licensure, have shown that varicella incidence rates are declining in children and adolescents regardless of vaccination status and that herpes zoster rates are no higher in vaccinated children compared with children with previous wild-type infection.

More than 49 studies have been conducted with VARIVAX™. In these clinical studies, VARIVAX™ has been administered to 28,772 participants, including 11,648 healthy children and 3257 healthy adolescents and adults who received only VARIVAX™ and 13,867 children who received VARIVAX™ concomitantly with other pediatric vaccines. VARIVAX™ was generally well tolerated. In a double-blind placebo-controlled study among 956 healthy children and adolescents, 914 of whom were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at a significantly greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site and varicella-like rash.

The safety results from the Phase 1 to 3 clinical studies are supported by the results of a large postmarketing study, which did not identify any significant vaccine-related adverse events (AEs) in more than 89,000 vaccinees, and by extensive postmarketing safety surveillance, which has not identified new safety signals, with approximately 226 million doses of VARIVAX™ distributed as of 16-MAR-2018. To date, VARIVAX™ has been licensed in over 60 countries, including countries in Europe and Asia. There is no evidence suggesting the response profile to VARIVAX™ differs across nationalities or ethnic groups.

In summary, vaccination with VARIVAX™ has been demonstrated to be highly efficacious against varicella infection, highly immunogenic, and generally well tolerated. The postmarketing safety profile continues to support the positive benefit/risk ratio of the vaccine.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on VARIVAX™.

2.2.1 VARIVAX™ and Varicella Disease

Varicella is a generalized illness with an incubation period of about 12 to 16 days, is highly contagious, and is characterized by a generalized, papulovesicular rash which typically resolves in 5 to 6 days. The most common complications of varicella include secondary bacterial infection, encephalitis, Reye syndrome, pneumonia, and death. Less common complications include nephritis, arthritis, orchitis, uveitis, thrombocytopenia, and purpura fulminans. Although immunity following varicella infection is generally long-lasting, the virus may persist in latent form in the peripheral nerve tissue (ganglia). Herpes zoster (or shingles) may develop as a result of the reactivation of latent VZV.

Before the introduction of a varicella vaccine (VARIVAX™), an estimated 4 million cases of varicella occurred annually in the United States (US) [Wharton, M. 1996], resulting in 10,000 yearly hospitalizations and over 100 deaths [Galil, K., et al 2002][Meyer, P. A., et al 2000]. VARIVAX™ was licensed in 1995 on the basis of studies that demonstrated single-dose efficacy of 70% to 95% against clinical disease and 95% against severe disease over a 7- to 10-year follow-up period [Kuter, B. J., et al 1991]. Following licensure, vaccine coverage has increased to an estimated 90% of the pediatric population in the US [Guris, D., et al 2008][Luman, Elizabeth T., et al 2006], reducing varicella incidence by up to 91% [Guris, D., et al 2008], and varicella-related hospitalizations by 75% to 88% [Zhou, Fangjun, et al 2005][Centers for Disease Control and Prevention, et al 2007]. During the first 12 years following licensure of VARIVAX™ in the US, the incidence of varicella-related mortality was reduced by 88%, including a 97% reduction in individuals under 20 years of age and a 96% reduction in individuals under 50 years of age [Marin, M., et al 2011]. Recent epidemiologic studies have demonstrated VARIVAX™ affords long-term protection over 15 years against varicella, and also imparts herd immunity to unvaccinated individuals in settings where vaccine adoption is widespread [Post-Licensure Studies to Evaluate the... 2010].

2.2.2 Preclinical and Clinical Studies

Refer to the IB for information on preclinical and clinical studies conducted with VARIVAX™.

2.2.3 Ongoing Clinical Studies

Refer to the IB for information on ongoing studies with VARIVAX™.

2.2.4 Information on Other Study-related Therapy

Refer to the IB for VARIVAX™.

2.3 Benefit/Risk Assessment

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

In the VARIVAX™ clinical development program, a single dose of VARIVAX™ has been shown to be highly efficacious in the prevention of varicella in children ≤12 years of age by multiple, complementary methods, including a placebo-controlled study, evaluation of the varicella attack rate following household exposure, and long-term follow-up of vaccinated cohorts in comparison to historical controls. Postvaccination breakthrough cases of varicella were significantly milder than wild-type disease. Studies with 2 doses of VARIVAX™ demonstrated a significant increase in vaccine efficacy as compared with a 1-dose regimen, regardless of whether the 2 doses were administered 3 months or 3 to 6 years apart. Although it is more difficult to estimate vaccine efficacy in adolescents/adults, administration of 2 doses of VARIVAX™ 4 to 8 weeks apart is associated with very low rates of postvaccination breakthrough disease and protection against household exposure to varicella. The data from the clinical development program are supported by postmarketing studies of vaccine effectiveness.

With approximately 226 million marketed doses of VARIVAX™ distributed worldwide from market introduction to 16-MAR-2018, the postmarketing safety profile continues to support the positive benefit/risk ratio of the vaccine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The following objectives and endpoints will be evaluated in Russian individuals 12 months to 75 years of age with a negative clinical history of varicella and/or herpes zoster. No formal hypotheses will be tested in the study.

Objectives	Endpoints
Primary	
Objective: To describe the immunogenicity of VARIVAX™ after: • Two doses of VARIVAX™, given 6 weeks apart, in adults 18 to 75 years of age (Stage 1). • Two doses of VARIVAX™, given 6 weeks apart, in adolescents 13 to 17 years of age (Stage 2). • One dose of VARIVAX™ in children 12 months to 12 years of age (Stage 2).	Participants who are seronegative at baseline (baseline VZV antibody titer <1.25 gpELISA units/mL): • Antibody response rate (percentage of participants with VZV antibody titer ≥5 gpELISA units/mL at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents/adults). • Geometric mean titers (GMTs) of VZV antibody as measured by gpELISA at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents/adults. • VZV seroconversion rate (percentage of participants with VZV antibody titer ≥1.25 gpELISA units/mL at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents/adults). Participants who are seropositive at baseline (baseline VZV antibody titer ≥1.25 gpELISA units/mL): • GMTs at Day 1 and 6 weeks postvaccination for children and at Day 1 and 6 weeks postdose 2 for adolescents/adults. • Geometric mean fold rise (GMFR) from Day 1 to 6 weeks postvaccination for children and from Day 1 to 6 weeks postdose 2 for adolescents/adults. • Percentage of participants with ≥4-fold rise in antibody titer from Day 1 to 6 weeks postvaccination for children and from Day 1 to 6 weeks postdose 2 for adolescents/adults.

Secondary	
Objective: To summarize the safety and tolerability of VARIVAX™.	Following each vaccination with VARIVAX™: • Solicited injection-site reactions (redness, swelling, and pain/tenderness) of any intensity or size from Day 1 through Day 5 postvaccination. • Unsolicited injection-site adverse events from Day 1 through Day 42 postvaccination. • Maximum reported temperature ≥39.0°C oral equivalent from Day 1 through Day 28 postvaccination. • Varicella-, and herpes zoster-like rashes occurring from Day 1 through Day 42 postvaccination. • Systemic adverse events from Day 1 through Day 42 postvaccination. • Serious adverse events from Day 1 through Day 42 postvaccination. Vaccine-related serious adverse events and death from Day 1 through the end of the study period (42 days following the last vaccination) for each participant. A summary of blood and urine tests performed 3 days following each vaccination for participants 7 years of age and older.

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, multicenter, single-arm bridging study to evaluate the immunogenicity of VARIVAX™ in healthy Russian individuals. This study will be conducted as a staged approach as outlined in Table 1, with approximately 150 participants. Participants 12 months of age to 75 years of age (inclusive) with a negative clinical history of varicella (ie, history of a generalized, pruritic, papulovesicular rash, often associated with fever) and/or herpes zoster (painful, dermatomal, papulovesicular rash), are eligible for enrollment in the study.

Note: The Stage 1 portion of the study will be conducted and completed first. The Stage 2 portion of the study will commence once an acceptable document for the Stage 1 portion of the study, such as a Clinical Study Report (CSR), has been submitted to the Russian Ministry of Health.

Enrollment will end when the minimum enrollment is attained for each age group as indicated in Table 1. For Stage 2, a minimum of 30 participants will be enrolled per age group, for a total of 100 participants overall.

Table 1 Study Design for Adults and Adolescents/Children

Intervention Groups	Target (Approximate) Enrollment (n)	VARIVAX™ Vaccination(s)	Duration (from first visit to last contact)
Stage 1 (n=50)			
Adults 18 to 75 years of age	50	2 doses given ~6 weeks apart	4 months
Stage 2 (n=100)			
Adolescents 13 to 17 years of age	Minimum 30	2 doses given ~6 weeks apart	4 months
Children 7 to 12 years of age	Minimum 30	1 dose	2 months
Children 12 months to 6 years of age	Minimum 30	1 dose	2 months

Serum samples will be obtained for evaluation of VZV antibody responses by gpELISA at baseline (Visit 1, prevaccination) and at 6 weeks following the last study vaccination (postvaccination for children 12 months to 12 years of age, and postdose 2 for adolescents/adults 13 to 75 years of age).

All participants will be followed for safety for 6 weeks (42 days) following each vaccination. For participants 7 years of age and older, blood samples for complete blood count (CBC) and blood chemistry and a urine sample for urinalysis will be collected prior to vaccination (Visit 1) and 3 days after each vaccination.

In addition, injection-site reactions and general AEs will be evaluated for all participants by an investigator or qualified designee 7 days (-2 days) after each vaccination.

A participant is considered to have completed the study when (1) has received the scheduled number of study vaccinations (1 dose for children or 2 doses for adolescents/adults), (2) all blood samples for the immunogenicity assessment have been collected, and (3) the 42-day safety data post each vaccination have been collected.

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

VARIVAX™ is not currently licensed in Russia. This study will describe the safety, tolerability and immunogenicity of VARIVAX™ in healthy Russian individuals, 12 months through 75 years of age, which represents the age range for which a license is sought. The purpose of this study is to generate sufficient clinical data for VARIVAX™ in the Russian population in order to demonstrate generalizability of the large amount of existing VARIVAX™ clinical data to the Russian population.

The study will be conducted as a staged approach study (2 stages):

Stage 1 participants are adults (n=50) with the age range of 18 years to 75 years (inclusive).

To ensure the age of the participants is well distributed across all age groups, the target enrollment of Stage 2 participants (n=100 total) will be as follows:

- Adolescent 13 to 17 years of age (minimum 30)
- Children 7 to 12 years of age (minimum 30)
- Children 12 months to 6 years of age (minimum 30)

As described below, the dose regimen, immunogenicity endpoints, and safety endpoints utilized in this study are consistent with those of past VARIVAX™ clinical studies. This will allow comparisons to existing global data, in order to bridge the safety, tolerability and immunogenicity of VARIVAX™ observed in global clinical studies to the Russian population.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

VZV seroconversion rates (measured by gpELISA), antibody response rates, and GMTs will be the primary endpoints of this study. These immunogenicity endpoints are consistent with those used in previous clinical studies of VARIVAX™. The primary time points for the immunogenicity analyses are 6 weeks postvaccination for children and 6 weeks postdose 2 for adolescents and adults, following completion of the indicated vaccination regimen for each age group.

4.2.1.2 Safety Endpoints

Clinical AEs defined in Section 3.0, which include solicited injection-site reactions, unsolicited injection-site AEs, serious adverse events (SAEs), and vaccine-related SAEs, will be the safety endpoints of this study. These safety endpoints are consistent with the labeled safety profile of VARIVAX™ in the US and European Union (EU), and with the safety endpoints used in previous clinical studies of VARIVAX™.

4.2.1.3 Future Biomedical Research

The Sponsor will conduct future biomedical research on buccal swab deoxyribonucleic acid (DNA) specimens and serum specimens collected during the study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

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. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant pharmacokinetic/pharmacodynamic relationships are observed or AEs are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to pharmacokinetic/pharmacodynamic results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical studies. 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. Additional informational material for Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) and investigational site staff is provided in Section 10.6.1.

4.3 Justification for Dose

In the US and EU, VARIVAX™ is indicated for active immunization for the prevention of varicella in individuals 12 months of age and older. VARIVAX™ is administered as a 0.5-mL subcutaneous dose, which is comprised of a minimum 1350 Plaque Forming Units (PFU).

In this study, 1 dose of VARIVAX™ will be administered to children 12 months to 12 years of age. Two doses of VARIVAX™ will be administered 6 weeks apart to adolescents and adults (13 to 75 years of age), as VARIVAX™ is less immunogenic in these age groups [Kuter, Barbara J., et al 1995].

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. 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).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the benefit/risk ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at particular study sites may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Healthy male and female participants with a negative clinical history of varicella and/or herpes zoster who are 12 months to 75 years of age (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

In order to be eligible for the study, the participant must:

1. Be 12 months to 75 years of age (inclusive), at the time of signing the informed consent/assent form.

2. Be in good health based on medical history (physical examination is not required).

3. Have a negative clinical history for varicella and herpes zoster.

Female participants of reproductive potential must:

4. Have a negative serum pregnancy test or urine pregnancy test (sensitive to 25 mIU/mL beta human chorionic gonadotropin [β-hCG]) prior to each study vaccination (on the day the participant is vaccinated and before vaccine is administered).

5. Agree to remain abstinent, or use (or have their partner use) 2 acceptable methods of birth control. Abstinence or 2 acceptable methods of birth control must be practiced or used from the day of enrollment, throughout the duration of the study, and continued until 3 months following the last study vaccination. In areas where abstinence is not a locally acceptable method of contraception, 2 acceptable methods of birth control must be used through 3 months following the last study vaccination. An acceptable method of birth control is defined as: intrauterine device (IUD), oral contraception, diaphragm with spermicide, contraceptive sponge, condom, vasectomy.

   Note: Female participants who are not of reproductive potential are eligible for the study without the use of contraceptives or pregnancy test. Female participants who are not of reproductive potential are defined as those who either (1) have not reached menarche; (2) have undergone hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or (3)

have reached menopause. Menopausal is defined as 1) no menses for >1 year but <3 years and confirmed by follicle stimulating hormone (FSH) levels elevated into the postmenopausal range, or 2) no menses for at least 3 years.

The participant OR the participant's legally acceptable representative must:

6. Understand the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent.

7. Provide consent for future biomedical research. However, enrollees may participate in the main study without participating in future biomedical research.

8. Be able to read, understand, and complete study questionnaires (eg, Vaccination Report Card [VRC]).

9. Be able to complete all scheduled visits and comply with the study procedures.

5.2 Exclusion Criteria

The participant must be excluded from the study if he/she:

1. Has a history of allergy or anaphylactic reaction to neomycin, gelatin, or any component of VARIVAX™ as listed in the IB.

2. Has received vaccination with any varicella or herpes zoster vaccine in either monovalent or combination form at any time prior to the study or is anticipated to receive one of these vaccines during the study.

3. Has received immune globulin, a blood transfusion or blood-derived products (does not include autologous blood/blood products) within 5 months prior to vaccination or plans to receive while enrolled in this study.

4. *Has received salicylates (eg, aspirin or any aspirin-containing products) within 14 days prior to vaccination.

5. *Has had an exposure to varicella or herpes zoster in the last 4 weeks prior to the study vaccination involving:

    1) Continuous household contact, or

    2) Playmate contact, (generally >1 hour of play indoors) or

    3) Hospital contact (in the same 2- to 4-bed room or in adjacent beds in a large ward or prolonged face-to-face contact with an infectious staff member or patient), or

    4) Contact with a newborn whose mother had onset of chickenpox 5 days or less before delivery or within 48 hours after delivery.

6. Has, or lives with a person who has, any congenital or acquired immune deficiency, neoplastic disease, or depressed immunity, including those resulting from corticosteroid use (see Exclusion Criterion #8 and Section 6.5 Concomitant Therapy) or other immunosuppressive therapy.

7. Has, or his/her mother or father has, a documented human immunodeficiency virus (HIV) infection, untreated syphilis infection, or viral hepatitis infection (Hepatitis B or Hepatitis C).

8. Has received 1) corticosteroids (systemic immunomodulatory steroids) (greater than the equivalent of 2 mg/kg total daily dose of prednisone [children] or greater than the equivalent of 20 mg total daily dose of prednisone [adolescents/adults]) for more than 5 consecutive days within 3 months prior to entering study, or 2) any dose of corticosteroids within 7 days prior to entering study, or 3) is expected to require corticosteroids (greater than 2 mg/kg total daily dose of prednisone [children] or greater than the equivalent of 20 mg total daily dose of prednisone [adolescents/adults] through the course of the study.

   Exception: Participants using non-systemic corticosteroids (eg, topical, ophthalmic, and inhaled) will be eligible for vaccination.

9. *Was vaccinated with a licensed, non-live vaccine (eg, Inactivated Poliovirus [IPV], Diphtheria, Tetanus, and Acellular Pertussis [DTaP], *Haemophilus influenzae* type b [Hib]) 30 days or less prior to vaccination or expected during the 42-day safety follow-up period postvaccination.

10. *Was vaccinated with any licensed live vaccine 30 days or less prior to any dose of the study vaccines or expected within the 42-day safety follow-up period postvaccination.

11. *Has a recent (<72 hours) febrile illness 38.9°C oral equivalent) prior to the study vaccination. Temperature may be converted to oral equivalent by adding 0.6°C to axillary temperatures and subtracting 0.6°C from rectal temperatures.

12. Is currently participating in (30 days or less prior to enrollment) or scheduled to participate in any other clinical study other than a surveillance study during the planned study period for this study.

13. Has any other underlying medical condition that, in the opinion of the investigator, may interfere with the evaluation of study objectives.

14. Is pregnant or nursing.

15. 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.

(If a participant meets any of the exclusion criteria marked with an asterisk (*), the Day 1 visit may be rescheduled for a time when these criteria are no longer met.)

5.3 Lifestyle Considerations

No special restrictions on diet or activity apply.

5.3.1 Vaccine Virus Transmission

Postmarketing experience with VARIVAX™ suggests that the varicella vaccine virus may rarely be transferred between healthy people who were vaccinated and developed a chickenpox-like rash, and healthy people who are not immune to chickenpox (those who have not had chickenpox, or the vaccine for chickenpox). Transfer of vaccine virus from people who were vaccinated and did not have a chickenpox-like rash has been reported. Therefore, vaccine recipients should attempt to avoid close contact with high-risk individuals who are not immune to chickenpox for up to 42 days after vaccination with VARIVAX™. In circumstances where contact with high-risk individuals cannot be avoided, the potential risk of transfer of vaccine virus should be weighed against the risk of getting and spreading natural chickenpox virus. Individuals with high-risk include:

1. Individuals with poor immune systems (such as individuals with leukemia, lymphoma, or HIV);

2. Pregnant women without documented history of chickenpox or laboratory evidence of prior infection;

3. Newborn infants of mothers without a documented history of chickenpox or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered 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 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 provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Open-label, single-dose vials of VARIVAX™ and Sterile Diluent for reconstitution will be supplied to the clinical sites. No participant-specific kitting is required.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level(s)	Route of Administration	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
1	Experimental	Varicella Virus Vaccine Live	Biological /Vaccine	Sterile Suspension after reconstitution	Refer to product labeling	0.5 mL	Subcutaneous	Adults 18-75 years of age and adolescents 13-17 years of age: 2 doses ~6 weeks apart ---------- Children 12 months to 12 years of age: 1 dose	Experimental	IMP	Provided centrally by the Sponsor
1	Experimental	Sterile Diluent for Reconstitution of Merck Live Virus Vaccines (Sterile Water)	Biological /Vaccine	Sterile Solution for Reconstitution	N/A	0.7 mL	Subcutaneous	N/A	Experimental	IMP	Provided centrally by the 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.

Varicella Virus Vaccine Live = VARIVAX™

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

The designated study site personnel will reconstitute the study vaccine using only the diluent provided by the Sponsor. The diluent for the vaccine is sterile distilled water and contains no preservatives or other substances that might inactivate the vaccine. To reconstitute the vaccine, first withdraw the entire contents of the diluent vial into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently swirl to mix thoroughly. Withdraw the entire contents into the syringe and inject the total volume (approximately 0.5 mL) of reconstituted vaccine subcutaneously (refer to Section 8.1.8 - Study Intervention Administration). Reconstituted vaccine should be administered within 30 minutes of removal from refrigerator.

Do not freeze reconstituted vaccine.

CAUTION: Sterile syringe should be free of preservatives, antiseptics, and detergents as these substances may inactivate the vaccine virus.

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

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.

6.2.3 Replacement Vials

A replacement vial of vaccine will be needed if an error is made in reconstituting the vaccine, if the reconstituted vaccine is not administered within 30 minutes of removal from the refrigerator, or if a vial of vaccine is accidentally destroyed or improperly handled. In this event, a small quantity of additional vials will also be available as replacement supplies. Complete and accurate information about these events must be reported and documented on the vaccine accountability log. The original treatment/randomization number assigned to the participant will not be changed. The original vial designated for use must be explained on the Clinical Supplies Return Form in the Administrative Binder.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

Minimum target enrollment by age group is presented in Table 1.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the vaccine administered.

6.4 Study Intervention Compliance

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 the ongoing study (see Section 5.2 for details). 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 or vaccination 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.

All medications administered from 14 days prior to study vaccination until 42 days following each study vaccination should be recorded on the appropriate case report form(s) (CRFs) or worksheet(s). Participants should not have received any previous varicella vaccine, either alone or in combination, or receive any such vaccines outside of study protocol for the duration of the study.

Other vaccines that are routinely administered should be given outside of the study period, at time points appropriate to those vaccines so as not to confound the results from this study. These vaccines will not be provided by the Sponsor or Sponsor designee. Enrollment in the study should be delayed if a medically important product needs to be administered. A full 30 days must elapse between the receipt of inactivated non-study (eg, pneumococcal conjugate, influenza, Hib) vaccines and enrollment into the study. A full 30 days must elapse between the receipt of live non-study vaccines (eg, measles, yellow fever) and enrollment into the study. Both inactivated and live non-study vaccines may be administered following the successful conclusion of study procedures (ie, completed safety follow-up period, and blood sample if indicated) at Visit 4 postvaccination [children] and Visit 7 postdose 2 [adolescents/adults].

Participants should not receive salicylates (eg, aspirin or any aspirin-containing products) from 14 days prior to vaccination until 42 days following the last study vaccination, because the use of salicylates in children and young adults with wild-type (natural) varicella infection has been associated with Reye syndrome.

Participants should not have received any immune globulin for at least 5 months (150 days) before receipt of study vaccine or be scheduled to receive these products within 12 weeks of enrollment unless there is a medical necessity warranting their use.

Use of immunosuppressive therapies is a reason for exclusion, with the following exceptions:

- Use of topical, ophthalmic, and inhaled steroids is permitted.

- Use of systemic corticosteroids must meet the following criteria:

- Participants should not have received systemic corticosteroids (greater than the equivalent of 2 mg/kg total daily dose of prednisone [children] or greater than the equivalent of 20 mg total daily dose of prednisone [adolescents/adults]) for more than 5 consecutive days within 3 months prior to entering the study;

- Participants should not receive any dose of systemic corticosteroids within 7 days prior to or following each vaccination;

- Participants should not receive systemic corticosteroids (greater than the equivalent of 2 mg/kg total daily dose of prednisone [children] or greater than the equivalent of 20 mg total daily dose of prednisone [adolescents/adults]) for more than 5 consecutive days from the time of study start through the end of the safety follow-up period.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

See Section 8.1.8 regarding administration of epinephrine in the event of an anaphylactic reaction.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification is specified to be used 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 open label; therefore, the participant, the study site personnel, the Sponsor and/or designee are not blinded. Vaccine (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Study site personnel will have access to a central electronic treatment allocation/randomization system (interactive voice response system [IVRS]/interactive web response system [IWRS]) to allocate participants, to assign vaccine to participants and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

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 protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in the SoA and Section 8.12.3.

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 and Section 8.12.3.

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 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 has a confirmed positive serum or urine pregnancy test.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

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

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. 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.

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

1. The participant or participant's legally acceptable representative withdraws consent from the study.

2. The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk through continued participation in the study or does not allow the participant to adhere to the requirements of the protocol.

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 Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- 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, and assent if applicable, 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 7 years of age and older over the duration of the study will not exceed 33 mL (Table 3). The maximum amount of blood collected from each participant 12 months to 6 years of age during the duration of the study will not exceed 10 mL (Table 4).

Table 3 Approximate Blood Drawn/Collected by Study Visit and by Sample Type – Participants 7 Years of Age and Older

Study Visit/Cycle/etc.	**Visit 1 Baseline Pre-vaccination 1**	**Visit 2 Post-vaccination 1**	**Visit 4 Post-vaccination 1 (children 12 months to 12 years)**	**Visit 5 Post-vaccination 2 (adolescents/ adults)**	**Visit 7 Post - vaccination 2 (adolescents/ adults)**
Blood Parameter	Volume (approximate)	Volume (approximate)	Volume (approximate)	Volume (approximate)	Volume (approximate)
Immunogenicity (VZV Antibody) Sample	3.0 to 5.0 mL		3.0 to 5.0 mL		3.0 to 5.0 mL
Safety (CBC and Blood Chemistry) Sample	6.0 mL	6.0 mL		6.0 mL	
Expected Total (mL)	9.0 to 11.0 mL	6.0 mL	3.0 to 5.0 mL	6.0 mL	3.0 to 5.0 mL

CBC = complete blood count; VZV = varicella-zoster virus
Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 4 Approximate Blood Drawn/Collected by Study Visit and by Sample Type – Participants 12 Months to 6 Years of Age

Study Visit/Cycle/etc.	Visit 1 Baseline Prevaccination	Visit 4 Postvaccination
Blood Parameter	Volume (approximate)	Volume (approximate)
Immunogenicity (VZV Antibody) Sample	3.0 to 5.0 mL	3.0 to 5.0 mL
Expected Total (mL)	3.0 to 5.0 mL	3.0 to 5.0 mL

VZV = varicella-zoster virus
Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples
Note: Safety laboratory samples are not applicable for participants 12 months to 6 years of age.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, 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 medically qualified designee must ensure the appropriate consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

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

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

The initial informed consent/assent form, any subsequent revised written informed consent/assent form, 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/assent form or addendum to the original consent/assent 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/assent form template at the protocol level.

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

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

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

Informed consent/assent for future biomedical research samples must be obtained before the collection of the buccal swab DNA samples.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

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/assent. 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. The eligibility of a participant will be assessed, and a medical history obtained to ensure that he/she satisfies the inclusion and exclusion criteria of the study. No physical exam is required for entry into the study.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 14 days before the first vaccination. A full 30 days must elapse between the receipt of inactivated non-study (eg, pneumococcal conjugate, influenza, Hib) vaccines and enrollment into the study. A full 30 days must elapse between the receipt of live non-study vaccines (eg, measles, yellow fever) and enrollment into the study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. All medications administered from 14 days prior to study vaccination until 42 days following each study vaccination should be recorded on the appropriate CRF(s)/worksheet(s).

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 intervention allocation. 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. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment number. The treatment number identifies the participant for all procedures occurring after treatment allocation. Once a treatment 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 number.

8.1.8 Study Intervention Administration

All participants who are 12 months of age to 12 years of age will receive 1 dose of VARIVAX™. Participants who are 13 years of age and older will receive 2 doses of VARIVAX™ administered approximately 6 weeks apart (see Section 1.3 – Schedule of Activities). Vials of vaccine will be labeled with treatment numbers and/or component identification numbers (CID) specific to each individual participant. Care should be taken to ensure that each participant receives the appropriate clinical materials labeled with their specific CID. This study will be conducted as a staged approach study. Administration of

study vaccine for Stage 2 participants (children/adolescents) will commence upon completion of Stage 1 (adults) portion of the study.

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist or medical assistant) as allowed by local, state, country and institutional guidance.

A separate, sterile syringe and needle or sterile disposable unit should be used for the administration of vaccine to each participant to prevent transmission of infectious agents from one person to another. Needles should not be recapped. Safe disposal procedures should be followed.

VARIVAX™ should be administered subcutaneously in the outer aspect of the upper arm (deltoid) or anterolateral thigh for children; in the outer aspect of the upper arm (deltoid) for adolescents/adults. All vaccinations and location of injection should be recorded on the appropriate CRF(s)/worksheet(s). Participants should be observed for anaphylaxis or other reactions for at least 30 minutes following vaccination (at least 60 minutes for children 3 years of age or younger).

Adequate treatment provision, including epinephrine and equipment for maintaining an airway should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

Protect the vaccine from light at all times since such exposure may inactivate the vaccine virus. It is recommended that the vaccine be administered immediately after reconstitution to minimize loss of potency.

Details of the vaccination, including the time the vaccine vial is removed from the refrigerator, the time of reconstitution, the time of administration of the vaccine, the site and route of administration, and the dose volume administered should be documented. If the reconstituted vaccine is not used within 30 minutes of removal from the refrigerator, a new vial will need to be reconstituted. Do not freeze reconstituted vaccine. Vials that are reconstituted and not used should be disposed of as biohazardous waste and noted on the Clinical Supplies Return Form located in the Administrative Binder.

8.1.8.1 Timing of Dose Administration

VARIVAX™ will be administered as indicated in the SoA (Section 1.3).

Participants who are 12 months of age to 12 years of age will receive one 0.5-mL subcutaneous dose of VARIVAX™ in the upper deltoid region of the arm or anterolateral thigh at Visit 1 on Day 1 of the study.

Participants who are 13 years to 75 years of age will receive a 0.5-mL subcutaneous dose VARIVAX™ in the upper deltoid region of the arm at 2 separate time points: Visit 1 and Visit 4.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study 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 8.3 and 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

This is an open-label study; there is no blinding for this study.

8.1.11 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

Serum samples will be tested for antibody to VZV using the gpELISA assay as described in Section 8.2.2. VZV seroconversion rates, antibody response rates, and GMTs will be used as

the primary immunogenicity endpoints in this study. The seroconversion rate for VZV is defined as the percentage of participants with VZV antibody titer ≥1.25 gpELISA units/mL in participants with a baseline VZV antibody titer <1.25 gpELISA units/mL. The antibody response rate for VZV is defined as the percentage of participants with a postvaccination VZV antibody titer ≥5 gpELISA units/mL for participants whose baseline VZV antibody titer was <1.25 gpELISA units/mL. Antibody titers ≥5 gpELISA units/mL have been shown to be highly correlated with long-term protection [Kuter, B., et al 2004].

8.2.1 Immunogenicity (VZV) Antibody Sample

For children, approximately 3.0- to 5.0-mL of blood will be collected prior to vaccination at Visit 1 (Day 1) and at Visit 4 (Day 43 [+14 days] postvaccination). For adolescents/adults, approximately 3.0- to 5.0-mL of blood will be collected prior to vaccination at Visit 1 (Day 1) and at Visit 7 (Day 43 [+14 days] postdose 2). The total amount of blood to be drawn/collected over the course of the study, including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Table 3 and Table 4. For all participants, the immunogenicity blood sample at Visit 1 (Day 1) is mandatory for enrollment. Any leftover serum will be stored for future biomedical research if the participant signs the future biomedical research consent. Instructions regarding the labeling, storage, and shipment of serum samples for laboratory measurements will be provided separately by the Sponsor or Sponsor designee in the laboratory manual. All serum specimens will be sent to the designated testing laboratory.

Levels of VZV antibodies will be measured at each of these time points for the entire study population. Serologic testing will be performed at the designated laboratory.

8.2.2 Detection of IgG Antibody to VZV (gpELISA)

The purpose of the gpELISA is to detect immunoglobulin G (IgG) antibody to VZV before and after vaccination with VZV-containing vaccine(s). This is the primary assay used by the Vaccines and Biologics Laboratory of PPD to evaluate the serological response to the vaccine(s). This method detects antibodies to VZV glycoprotein (gp), which has been purified from Medical Research Council cell strain 5 (MRC-5) cells infected with the KMcC strain of VZV by lectin affinity chromatography. The reactivity of the sera to the gp antigens from uninfected MRC-5 cells (denoted as Tissue Culture Control [TCC] wells]) is subtracted from the reactivity of the sera to the gp antigens purified from VZV-infected MRC-5 cells. The assay and the purification of the VZV gp from VZV-infected cells are described [Keller, P. M., et al 1986][Wasmuth, E. H. and Miller, W. J. 1990][Provost, P. J., et al 1991]. Serum sample titers as determined by gpELISA are shown to correlate with neutralizing antibody titers [Krah, D. L., et al 1997].

For the gpELISA, VZV gp or TCC antigen is adsorbed to polystyrene microtiter wells and used as the solid phase antigen. Experimental, control, and standard curve sera are incubated in VZV gp-coated and TCC-coated wells (2 wells for each antigen). For each serum sample, a delta optical density (DOD) is calculated as the difference between the average optical density (OD) of the 2 VZV antigen wells and the average optical density (OD) of the 2 TCC

wells. Quantitation is obtained by comparison of sample DOD with a standard curve. Results for the assay are reported as concentration of antibody in gpELISA units/mL.

The negative control used for this assay is an individual human serum at a dilution of 1:50, found to be negative for anti-VZV. The high-positive control is a VZV antibody-positive serum, diluted 1:500, which gives a response in the assay at the upper end of the standard curve. The low-positive control is a VZV antibody-positive serum diluted 1:50, which gives a response in the assay at the lower end of the standard curve. A VZV antibody-positive individual human serum will be used to generate a standard curve.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study, including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Table 3 and Table 4.

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

8.3.1 Safety Assessments and Use of the VRC

Unless otherwise stated, all AEs will be collected for 42 days following each vaccination with VARIVAX™ using a VRC as detailed in Section 8.4.

Each participant or participant's legally acceptable representative will be given a VRC following vaccination and will be instructed to record the safety data on the VRC. The VRC is required to be completed for a full 42 days following each vaccination. The participant or the participant's legally acceptable representative will return the completed VRC to the site at the visit on Day 43 (+14 days) following each vaccination.

On Days 7 and 43 following each vaccination study personnel will review the information with the participant or the participant's legally acceptable representative for completeness, accuracy, and clarity. All information will be accurately recorded on the appropriate CRFs/worksheets.

The following AEs will be recorded on the VRC and reported for all participants:

- Solicited local (injection-site) AEs for Days 1 to 5 following vaccination. Solicited local (injection-site) AEs include redness, swelling, and pain/tenderness. The maximum intensity (mild, moderate, or severe) for pain/tenderness and the maximum size (using a scale provided on the VRC) for redness and swelling will be recorded on the VRC (refer to Section 10.3.6).

- Unsolicited injection-site AEs regardless of severity or causality through Day 42 following vaccination.

- The participant's temperature, including the route used to measure the temperature (oral, axillary or rectal [according to the local standard of care for temperature measurement]), 4 to 6 hours postvaccination and then daily, preferably at the same time each day, through Day 28 following vaccination.

    - For participants <3 years of age, it is recommended that the temperature be measured by the axillary method. The temperature reading including the route used to measure the temperature, must be recorded in the VRC. Study personnel should advise the participant's legally acceptable representative on the proper manner in which to measure axillary temperatures to ensure that accurate measurements are obtained.

    - For participants ≥3 years of age it is recommended that the temperature be measured using the oral method; however, the local standard of care method of temperature measurement may be used as an alternative method.

- The development of varicella-like and herpes zoster-like rashes through 42 days following vaccination. The participant or the patient's legally acceptable representative will be instructed to contact study personnel immediately if the participant develops a varicella- or herpes zoster-like rash during the 42-day safety follow-up periods. Participants should be seen at the clinic within 72 hours of the rash presentation. Study personnel will review the completed VRC to identify any unreported occurrences of these vaccine virus-specific conditions.

- The occurrence of all systemic AEs regardless of severity or causality through Day 42 following vaccination.

- SAEs occurring at any time from study enrollment through study completion. These events should be reported immediately to study personnel regardless of causality. Study personnel should report any SAE within 24 hours to one of the individuals listed on the sponsor contact information page in the Administrative Binder.

- Vaccine-related SAEs and death from study start through the end of the study for each participant (Day 42 following the last vaccination).

8.3.2 Clinical Safety 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 or medically qualified designee (consistent with local requirements) 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 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 42 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.

8.3.2.1 Serum or Urine Pregnancy Test

Female participants of reproductive potential (See Inclusion Criterion #4) will have a serum pregnancy test or urine pregnancy test sensitive to 25 mIU/mL β-hCG administered on the day of the first vaccination. For female participants of reproductive potential, another serum pregnancy test or urine β-hCG pregnancy test will also be performed on the day of the second vaccination. Pregnancy test results must be obtained before study vaccine is administered. All materials used for serum and urine pregnancy testing will be provided by the study sites. The serum pregnancy test or the urine pregnancy test will be performed according to the manufacturer's instructions. Any participant with a positive pregnancy test result at Day 1 (Visit 1) will not participate in the study. Any participant with a positive pregnancy test at or prior to Visit 4 will not receive the second study vaccination.

8.3.2.2 Laboratory Measurements – CBC, Chemistry and Urinalysis

Participants 7 years of age and older will have approximately 2.0 mL of whole blood drawn for CBC, approximately 4.0 mL of whole blood drawn for blood chemistry, and urine collected for urinalysis including macroscopic plus microscopic evaluation (see Appendix 2).

For participants 7 to 12 years of age, blood (approximately 6 mL) and urine will be collected at 2 time points: prior to vaccination (Visit 1), and 3 days postvaccination. For adolescents and adults 13 to 75 years of age, blood (approximately 6 mL) and urine will be collected at 3 time points: prior to vaccination (Visit 1), and 3 days after each of the 2 vaccinations.

The total amount of blood/tissue to be drawn/collected for safety laboratory assessments over the course of the study, including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in Table 3.

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. Note: Rechallenge is not applicable for this study.

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 and any designees are responsible for detecting, 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 AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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 42 days following the first vaccination(s) and from the time of any subsequent vaccination(s) through 42 days thereafter, all AEs, SAEs, and other reportable safety events must be reported by the investigator. Pregnancy exposure and infant exposure during lactation must be reported to the sponsor through 3 months post each vaccination.

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:

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

OR

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

Investigators are not obligated to actively seek AEs or SAEs 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 5.

Table 5 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	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious 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	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	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	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 AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), 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. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study (within 3 months following vaccination) are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

Not applicable.

8.4.7 Events of Clinical Interest (ECIs)

Selected non-serious and SAEs are also known as events of clinical interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent/assent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 5 calendar days to the Sponsor if it causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 42 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 5 calendar days to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the electronic data collection (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5 - Definition and Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

8.5 Definition and Treatment of Overdose

In this study, an overdose is any dose greater than one dose of study vaccine within 24 hours.

If an AE is associated with ("results from") the overdose of Sponsor's product or vaccine, the AE is reported as an SAE, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported by the investigator within 5 calendar days to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Pharmacokinetic 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

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

- Buccal swabs for genomics use. Buccal swab DNA samples for analysis should be obtained prior to vaccination, on Day 1, or at a later date as soon as the informed consent/assent is obtained.

- Leftover serum immunogenicity samples collected in the main study.

8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.10 Biomarkers

Biomarkers will not be evaluated in this study.

8.11 Health Economics Medical Resource Utilization and Health Economics

Health Economics OR Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

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

8.12.1 Screening

Prior to intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

8.12.2 Treatment Period/Vaccination Visit

Specific procedures to be performed during the treatment period, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3

8.12.3 Discontinued Participants Continuing to be Monitored in 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 protocol-specified treatment period/vaccination regimen will still continue to participate in the study.

8.12.4 Poststudy

Participants will be required to return to clinic approximately 42 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 42 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 42 days (+14 days) post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any database lock, changes are made to primary and/or key secondary analyses, or the statistical methods related to those analyses, then the protocol will be amended (consistent with International Council for Harmonisation [ICH] Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The Stage 1 portion of the study will be conducted and

completed first. The Stage 2 portion of the study will commence once the CSR for Stage 1 has been submitted to the Russian Ministry of Health. A separate CSR for the Stage 2 portion of the study will be submitted to the Russian Ministry of Health when Stage 2 is completed.

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 through 9.12.

Study Design Overview	An open-label, multicenter, single-arm study to evaluate the immunogenicity of VARIVAX™ in healthy Russian individuals 12 months of age to 75 years of age
Treatment Assignment	All participants will receive VARIVAX™
Analysis Populations	**Immunogenicity**: Per-Protocol (PP) **Safety**: All-Participants-as-Treated (APaT)
Primary Endpoint(s)	• For participants who are seronegative at baseline, VZV antibody response rate, seroconversion rate, and GMTs will be summarized at 6 weeks following vaccination for children, and at 6 weeks postdose 2 for adolescents/adults. • For participants who are seropositive at baseline, following endpoints will be summarized at Day 1 and 6 weeks postvaccination for children and at Day 1 and 6 weeks postdose 2 for adolescents/adults: GMTs, GMFR from Day 1 to 6 weeks postvaccination, and the percentage of participants with ≥4-fold rise in antibody titer from Day 1 to 6 weeks postvaccination.
Key Secondary Endpoints	• Solicited injection-site reactions (redness, swelling, and pain/tenderness) of any intensity or size from Day 1 through 5 postvaccination for children and from Day 1 through 5 postdose 1 and 2 for adolescents/adults. • Maximum reported temperature ≥39.0°C oral equivalent from Day 1 through Day 28 postvaccination for children and from Day 1 through Day 28 postdose 1 and 2 for adolescents/adults. • Systemic AEs from Day 1 through Day 42 postvaccination for children and from Day 1 through Day 42 postdose 1 and 2 for adolescents/adults. • Vaccine-related SAEs and death from Day 1 through the end of the study period (42 days following the last vaccination) for each participant.
Statistical Methods for Key Immunogenicity Analyses	No formal hypothesis will be tested. VZV immunogenicity will be summarized separately for adults, adolescents, and children. Exact one-sample binomial distribution will be used to estimate the response rate, seroconversion rate, and the associated 95% confidence intervals (CIs). The estimation of GMTs and the computation of corresponding 95% CIs will be calculated using t-distribution for one-sample mean based on log-transformed titers.
Statistical Methods for Key Safety Analyses	No formal hypothesis will be tested. Summary statistics for safety endpoints listed in Section 3 will be provided.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is required for this study

Sample Size and Power	**Immunogenicity:** No formal power calculation for immunogenicity was performed to determine the current sample size. Section 9.9.1 provides information about the expected precision of estimation for response rates and GMTs under different sample size. **Safety:** Section 9.9.2 provides information about the ability of this study to estimate the incidence of vaccine-related SAEs within the vaccination group based on hypothetical number of participants.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the designee/Clinical Biostatistics department of the Sponsor.

This study (through completion of the 42 days of each postvaccination safety follow-up period) will be conducted as an open-label, single-arm study, ie, participants, investigators, and Sponsor personnel will be aware of vaccination assignments after each participant is enrolled and the vaccination is assigned.

The allocation schedule will be generated by an external vendor.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. No formal hypotheses will be tested in this study.

9.4 Analysis Endpoints

9.4.1 Immunogenicity Endpoints

The immunogenicity endpoints for VZV are:

- The response rates (defined as the percentage of participants with VZV antibody titer ≥5 gpELISA units/mL) 6 weeks postvaccination [for children] or 6 weeks postdose 2 [for adolescents/adults] among participants who are seronegative to VZV at baseline (titer <1.25 gpELISA units/mL).

- GMTs of VZV antibody as measured by gpELISA.

- The seroconversion rates (defined as the percentage of participants with VZV antibody titer ≥1.25 gpELISA units/mL) 6 weeks postvaccination [for children] or 6 weeks postdose 2 [for adolescents/adults] among participants who are seronegative to VZV at baseline (titer <1.25 gpELISA units/mL).

- For participants who are seropositive at baseline (baseline VZV antibody titer ≥1.25 gpELISA units/mL), the GMFR from Day 1 and the percentage of participants with ≥4-fold rise in antibody titer from Day 1 will be summarized at Day 1 and 6 weeks postvaccination for children and 6 weeks postdose 2 for adolescents/adults.

Immunogenicity summaries will be provided at Day 1 for all participants, at 6 weeks following vaccination for children, and at 6 weeks postdose 2 for adolescents and adults separately.

9.4.2 Safety Endpoints

The safety endpoints are:

- Solicited injection-site reactions (redness, swelling, pain/tenderness) of any intensity or size from Days 1 through 5 following each vaccination.
- Unsolicited injection-site AEs, regardless of severity or causality, from Day 1 through Day 42 of each postvaccination.
- Maximum reported temperature ≥39.0°C oral equivalent from Day 1 through Day 28 following each vaccination. Recorded temperatures will be converted to oral equivalents by adding 0.6°C to axillary temperatures and subtracting 0.6°C from rectal temperatures.
- Varicella-, and herpes zoster-like rashes occurring from Day 1 through Day 42 following each vaccination.
- Systemic AEs from Day 1 through Day 42 following each vaccination.
- SAEs from Day 1 through Day 42 following each vaccination.
- Vaccine-related SAEs and death from Day 1 through the end of the study for each participant (Day 42 following the last vaccination).
- A summary of blood and urine tests performed 3 days following each vaccination for participants 7 years of age and older

Unless otherwise stated, all AEs will be collected for 42 days postvaccination after each dose of VARIVAX™.

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The Per-Protocol (PP) population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all allocated participants without deviations from the protocol that may substantially affect the results of the

immunogenicity endpoint(s). Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Missing either a baseline or postvaccination blood sample.
- Deviations from of inclusion/exclusion criteria, including:
    - Recent exposure (<4 weeks) to varicella or herpes zoster prior to vaccination (duration of exposure as defined in Section 5.2) or prior to the completion of clinical and serological follow-up in this study (exclusion from the PP population would only affect data collected subsequent to the deviation).
    - History of varicella or herpes zoster prior to study entry, or development of varicella prior to the completion of clinical and serological follow-up in this study (exclusion from the PP population would only affect data collected subsequent to the deviation).
    - Receipt of varicella or herpes zoster vaccine either alone or in combination at any time prior to the study or during the study.
    - Receipt of immune globulin, a blood transfusion, or blood-derived products (does not include autologous blood/blood products) within 5 months (150 days) prior to receipt of a study vaccine, or receipt of these products prior to completion of clinical and serological follow-up in this study (exclusion from the PP population would only affect data collected subsequent to the deviation).
    - Age of participant at study entry is <12 months. (Deviations of the lower age limit will result in exclusion from the PP population due to the potential presence of maternal antibody, which might interfere with the evaluation of the vaccine response).
    - Any congenital or acquired immune deficiency, neoplastic disease, or depressed immunity, including those resulting from steroid use or other immunosuppressive therapy (see Section 8.1.5.2 for definition of steroid use warranting exclusion).
- Postvaccination blood sample is outside the allowable day range, which is 27 to 84 days after the associated dose of vaccine was administered for 6-week serology samples. This window for inclusion of samples in the statistical analysis is wider than the window provided earlier in this protocol (+14 days for the 6-week serology testing); however, it is being used to be consistent with other studies evaluating VZV containing vaccines.
- Participant is participating in another clinical study (other than a surveillance study).

- In addition, the primary analysis requires specific baseline criteria be met for VZV: antibody titer (<1.25 gpELISA units/mL).

The final determination on major protocol deviations, and thereby the composition of the PP population, will be made prior to the finalization of the database and will be documented in a separate memo.

A supportive analysis using the Full Analysis Set (FAS) population will also be performed for the immunogenicity endpoints. The FAS population consists of all allocated participants who received all study vaccinations required at the time point for the analysis and have serology result.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the All-Participants-as-Treated (APaT) population, which consists of all allocated participants who received at least one dose of study vaccine and who have some safety follow-up data after respective vaccination.

For participants 7 years of age or older, at least one laboratory measurement obtained subsequent to at least one dose of study vaccination is required for inclusion in the analysis of the respective safety parameter. For all participants, at least one temperature measurement obtained subsequent to at least one dose of study vaccination is required for inclusion in the analysis of the maximum temperature. To assess change from baseline, a baseline measurement is also required.

9.6 Statistical Methods

Statistical methods for immunogenicity and safety analyses are described in Section 9.6.1 and Section 9.6.2, respectively. No formal hypothesis will be tested in this study.

Section 9.6.3 describes how demographic and baseline characteristics will be summarized.

9.6.1 Statistical Methods for Immunogenicity Analyses

Immunogenicity summaries will be provided at baseline (prevaccination) for all participants, and at 6 weeks postvaccination for children, at 6 weeks postdose 2 for adolescents, and at 6 weeks postdose 2 for adults. The primary time points for immunogenicity summaries will be 6 weeks postvaccination for children and 6 weeks postdose 2 for adolescents/adults. For each interval, immunogenicity will be evaluated by determining baseline and postvaccination serum concentrations of VZV antibody measured by gpELISA.

The first endpoint that will be used to evaluate the immunogenicity of VARIVAX™ is response rate, which is defined as the percentage of participants with VZV-specific antibody titer ≥5 gpELISA units/mL 6 weeks postvaccination for children and 6 weeks postdose 2 for adolescents/adults, in participants who have a VZV–specific antibody titer of <1.25 gpELISA units/mL at baseline. A 95% CI for this endpoint will be calculated using the exact CI method for a single binomial proportion given in Collett [Collett, D. 1999].

The second endpoint that will be used to evaluate the immunogenicity of VARIVAX™ is the GMT. The GMT will be calculated at each time point by taking the log of the titers, averaging over all participants values, and then back-transforming to the original scale. A 95% CI for the GMTs will be calculated based on the t-distribution.

The third endpoint that will be used to evaluate the immunogenicity of VARIVAX™ is the seroconversion rate. The observed VZV seroconversion rate (the percentage of participants with VZV titer ≥1.25 gpELISA units/mL 6 weeks postvaccination for children and 6 weeks postdose 2 for adults, in participants who have a VZV–specific antibody titer of <1.25 gpELISA units/mL at baseline) will be summarized along with two-sided 95% CIs. The CIs will be computed using the exact method for a single binomial proportion given in Collett [Collett, D. 1999]. This will be computed on the PP population of participants (restricted to those with baseline titer <1.25 gpELISA units/mL) and on the FAS population (regardless of baseline status).

For participants in the PP population only, graphical displays of the reverse cumulative distribution function of antibody titers will be illustrated at 6 weeks postvaccination for children and 6 weeks postdose 2 for adolescents/adults.

Table 6 summarizes the key immunogenicity analyses. For participants who are seropositive at baseline (baseline VZV antibody titer ≥1.25 gpELISA units/mL), the following parameters and 95% CIs will be summarized at Day 1 and 6 weeks postvaccination for children and 6 weeks postdose 2 for adolescents/adults: the GMTs, the GMFR from Day 1, and the percentage of participants with ≥4-fold rise in antibody titer from Day 1. CIs will only be calculated if there are at least 5 participants who are seropositive at baseline in a given age stratum.

Table 6 Primary Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	**Primary vs. Supportive Approach**	**Statistical Method**	**Analysis Population**	**Missing Data Approach**
Summaries of response rates at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents and adults, separately	P	Exact One-Sample Binomial; corresponding 95% CIs	PP	Observed data only
	S		FAS	
Summaries of GMTs at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents and adults, separately	P	One-sample mean and 95% CI based on log-transformed titers and t-distribution	PP	Observed data only
	S		FAS	
Summaries of seroconversion rates at 6 weeks postvaccination for children and at 6 weeks postdose 2 for adolescents and adults, separately	P	Exact One-Sample Binomial: methodology, 95% CIs	PP	Observed data only
	S		FAS	
CI = confidence interval; GMT = geometric mean titer; FAS = Full Analysis Set; P=Primary approach; PP = Per Protocol; S=Secondary approach.				

9.6.2 Statistical Methods for Safety Analyses

The APaT population will be employed for safety analyses. Safety analyses will be presented by Stage, and within Stage, Postdose 1, Postdose 2, and Postdose 1 or 2. All participants vaccinated and who have safety follow-up data will be included in the analysis of safety. Clinical AEs for 42 days following each of the study vaccination and the number and proportion of participants with the following clinical AEs will be tabulated as follows:

- Solicited injection-site reactions (redness, swelling, and pain/tenderness) of any intensity or size from Days 1 through 5 postvaccination for children and from Days 1 through 5 postdose 1 and 2 for adolescents/adults.

- Unsolicited injection-site AEs, regardless of severity or causality, from Day 1 through Day 42 postvaccination for children and from Days 1 through 42 postdose 1 and 2 for adolescents/adults.

- Maximum reported temperature ≥39.0°C oral equivalent from Day 1 through Day 28 postvaccination for children and from Days 1 through 28 postdose 1 and 2 for adolescents/adults.

- Varicella- and herpes zoster-like rashes occurring from Day 1 through Day 42 postvaccination for children and from Days 1 through 42 postdose 1 and 2 for adolescents/adults.

- Systemic AEs from Day 1 through Day 42 postvaccination for children and from Days 1 through 42 postdose 1 and 2 for adolescents/adults.

- SAEs from Day 1 through Day 42 postvaccination for children and from Days 1 through 42 postdose 1 and 2 for adolescents/adults.

- Vaccine-related SAEs and death from Day 1 through the end of the study (Day 42 following the last vaccination).

Unless otherwise stated, all AEs will be collected for 42 days postvaccination after each dose of VARIVAX™.

In addition, all CBC, blood chemistry and urinalysis data collected at Visit 1 and 3 days postvaccination for participants 7 years of age and older, will be summarized at all time points that these laboratory data are collected. However, no formal statistical testing will be conducted.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Participant characteristics of age, gender, and race/ethnicity will be summarized for all participants who enter the study. In addition, baseline serostatus for VZV will be presented.

The number (%) of participants with specific prior medications (incidence rate >0%) within 14 days prior to the vaccination will be summarized.

The number (%) of participants with specific concomitant medications (incidence rate >0%) within 42 days following each vaccination will be summarized.

A detailed participant accounting will be provided. This accounting will describe the number of participants allocated at study start, the number vaccinated at the vaccination visit, and the number of discontinuations and withdrawals during the safety follow-up period. This participant accounting will also indicate the number of participants who completed the study.

No other analyses are planned for this study.

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

No multiplicity adjustment is required for this study.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

Since this is an estimation study, no formal power calculation for immunogenicity was performed to determine the current sample size. However, the expected precision of estimation is given below. For immunogenicity summaries, the response rates and the associated 95% CI under different sample sizes of the adult, adolescents and children PP populations are estimated and presented in Table 7. In addition, the expected precision of the GMTs under different sample sizes of the adult and adolescents and children PP populations is presented in Table 8.

Table 7 Response Rates and Associated 95% CI Based on Different Sample Sizes of Per-Protocol Population

Population	Sample Size of Per-Protocol Population	Hypothetical Response Rate	95% Confidence Interval	
			Lower	Upper
Adult	40	0.80	0.64	0.91
		0.85	0.70	0.94
		0.90	0.76	0.97
	45	0.80	0.65	0.90
		0.84	0.71	0.94
		0.91	0.79	0.98
Adolescent	25	0.80	0.59	0.93
		0.84	0.64	0.95
		0.92	0.74	0.99
	30	0.80	0.61	0.92
		0.83	0.65	0.94
		0.90	0.73	0.98
Children	55	0.80	0.67	0.90
		0.85	0.74	0.94
		0.91	0.80	0.97
	60	0.80	0.68	0.89
		0.85	0.73	0.93
		0.90	0.79	0.96

Table 8 Expected Precision of GMTs under Different Sample Sizes of Per-Protocol Population

Population	Sample Size of Per-Protocol Population	Hypothetical GMT	95% Confidence Interval	
			Lower	Upper
Adult (Postdose 2)	40	80.0	58.1	110.1
		100.0	72.6	137.7
		120.0	87.2	165.2
	45	80.0	59.2	108.0
		100.0	74.0	135.0
		120.0	88.9	162.1
Adolescent (Postdose 2)	25	80.0	52.9	120.9
		100.0	66.2	151.1
		120.0	79.4	181.3
	30	80.0	55.1	116.2
		100.0	68.8	145.3
		120.0	82.6	174.3
Children (Postvaccination)	55	10.0	7.6	13.1
		12.0	9.2	15.7
		14.0	10.7	18.3
	60	10.0	7.7	12.9
		12.0	9.3	15.5
		14.0	10.8	18.1
Based on an assumed standard deviation of the 1.0 for the log antibody titers.				

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with an SAE in the study population. In Stage 1, it is expected that approximately 50 participants will contribute to the analysis of safety Postdose 1. In Stage 2, it is expected approximately 100 participants will contribute to the analysis of safety Postdose 1.

If no serious vaccine-related AEs are observed in this study in Stage 1 with 50 participants evaluable for safety, there will be a 97.5% probability that the true incidence rate is no more than 7.1%. If no serious vaccine-related AEs are observed in this study in Stage 2 with 100 children/adolescents in this study evaluable for safety, there will be a 97.5% probability that the true incidence rate is no more than 3.6%. The estimate of and the upper bound of the 95% CI for the underlying percentage of participants with a serious vaccine- related AEs given various hypothetical observed number of participants with a serious vaccine-related AEs among approximately 50 adult and approximately 100 adolescents/children are provided in Table 9.

Table 9 Estimate of Incidence of Vaccine-Related Serious Adverse Events and Upper Bound of 95% Confidence Interval Based on Hypothetical Number of Participants with Vaccine-Related Serious Adverse Events

Population	Sample Size	Hypothetical Number of Participants With VR-SAE	Estimate of Incidence	Upper Bound of 95% Confidence Interval †
Adult	50	0	0.0%	7.1%
		1	2.0%	10.7%
		2	4.0%	13.7%
Adolescent/children	100	0	0.0%	3.6%
		1	1.0%	5.4%
		2	2.0%	7.0%

† Based on the two-tailed exact CI of a binomial proportion given in Collett [Collett, D. 1999].
VR-SAE = vaccine-related serious adverse event

9.10 Subgroup Analyses

For participants enrolled in the Stage 2 portion of the study, a summary of immunogenicity and safety endpoints will be provided based on following variables:

- Age: 12 months to 6 years, 7 to 12 years, and 13 to 17 years of age
- Dosing schedule:
    - participants receiving 1 dose of VARIVAX™ (12 months to 12 years of age)
    - participants receiving 2 doses of VARIVAX™ (13 to 17 years of age)

9.11 Compliance (Medication Adherence)

The number and proportion of allocated participants receiving each vaccination will be summarized (Section 9.12).

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of allocated participants administered VARIVAX™ at each scheduled vaccination.

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 (Institutional 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 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 Debarment

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 GCP); 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. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution 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

The tests detailed in Table 10 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	WBC count with differential
	Hemoglobin
	Hematocrit
	Platelet Count
Chemistry	Sodium
	Potassium
	Chloride
	CO_2/Bicarbonate
	Blood Urea Nitrogen
	Creatinine
	Glucose (nonfasting)
Routine Urinalysis	• Macroscopic panel: Appearance, Bilirubin, Blood, Color, Glucose, Ketones, Leukocyte Esterase (LE), Nitrites, pH, Protein, Specific Gravity, Urobilinogen • Microscopic panel (reflex test): Amorphous Crystals, Bacteria, Calcium Carbonate Crystals, Calcium Oxalate Crystals, Calcium Phosphate Crystals, Cysteine Crystals, Granular Casts, Hyaline Casts, RBC, RBC Casts, Renal Epithelial Cells, Squamous Epithelial Cells, Transitional Epithelial Cells, Uric Acid Crystals, WBC and WBC Casts
Other Screening Tests	Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP)
NOTES: All study-required laboratory assessments will be performed by a central laboratory, with the exception of the serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP). RBC = red blood cells; WOCBP = woman/women of childbearing potential	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), 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 used 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 redness, swelling, or hard lump from the day of vaccination through Day 4 postvaccination will be evaluated by maximum size (Section 10.3.6).

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 CRF/worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed 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 (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite 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 drug-induced effect (applies to studies with investigational medicinal product)?

- **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.

- **Dechallenge**: Not applicable for vaccines.

- **Rechallenge**: Was the participant re-exposed to the Sponsor' s product in this 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 drug 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 AEs, SAEs, 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).

10.3.6 Assessment of Injection-Site Complaints or Reactions

The following instructions are excerpted from the Vaccination Report Cards (VRCs) and are included for reference only. Refer to the complete VRC provided when performing the actual measurements.

A. Adolescent/Adult Vaccination Report Card (Over 13 Years of Age)

Swelling and Redness

To Measure Swelling: Look at the injection site complaint and determine what area of the swollen region is the largest. Place the VRC-provided ruler on the edge of where the swollen area begins across to where it ends (measuring in whatever direction is the largest area). Use the VRC-provided ruler marks to determine which letter area (A through E→) the swelling falls into.

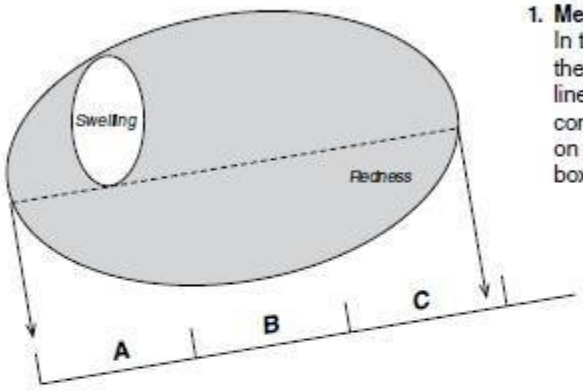
To Measure Redness: Look at the injection site complaint and determine where the red area is the largest. Place the VRC-provided ruler on the edge of where the red area begins across to where it ends (measuring in whatever direction has the largest area). Use the VRC-provided ruler marks to determine which letter are (A thru E→) the redness falls into.

Mark the boxes that best describe the size of the swelling and/or redness complaints;

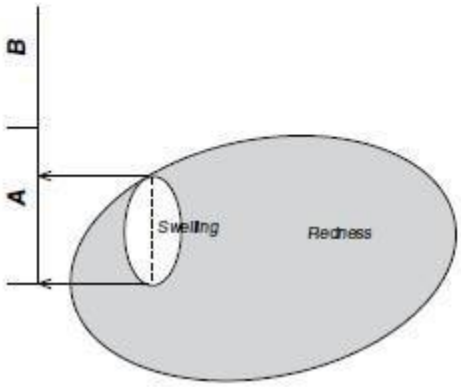
- **None** if there is no swelling or redness at the injection site
- **A** if the greatest width is anywhere in the area marked A
- **B** if the greatest width is anywhere in the area marked B
- **C** if the greatest width is anywhere in the area marked C
- **D** if the greatest width is anywhere in the area marked D
- **E** or greater if the greatest width is anywhere in the area marked E→

EXAMPLE

The images below are examples of an injection site complaint. In these pictures, the **white area** is the **swollen** area and the **dark area** is the area of the complaint that is **red**.



1. **Measuring the size of Redness**
In this complaint, the largest area of the **redness** is shown by the dashed line. As the arrows show, this complaint falls in the area marked "C" on the ruler, so you would check the box marked "C".



2. **Measuring the size of Swelling**
In this complaint, the largest **swollen** area is shown by the dashed line. As the arrows show, this complaint falls in the area marked "A" on the ruler, so you would check the box marked "A".

Pain or Tenderness or Other Reactions

Mark the box that best describes the severity of the complaint using the following definitions:

- **None** is if you do not experience any pain or tenderness
- **Mild** is awareness of symptom, but easily tolerated
- **Moderate** is discomfort enough to cause interference with usual activities
- **Severe** is inability to do work or usual activities

B. Pediatric Vaccination Report Card (3-13 Years of Age)

Swelling and Redness

Estimate the size of the reaction at its largest from edge to edge. Use the VRC-provided ruler marks along the bottom of the page

Mark the box that best describes the size of the reaction:

- **1** if the greatest width is anywhere in the area marked 1 (**Example A**)
- **2** if the greatest width is anywhere in the area marked 2
- **3** if the greatest width is anywhere in the area marked 3 (**Example B**)
- **Over 3** if the greatest width is in any area marked with a number over 3. Write in the number (**Example C**)
- If the reaction is wider than the area marked 7, write in 8.

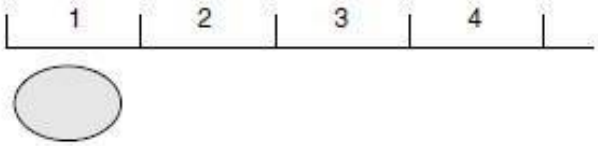
Pain or Tenderness or Other Reactions

Mark the box that best describes the severity of the reaction using the following definitions:

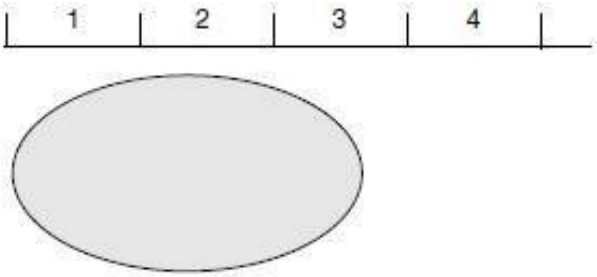
- **Mild** is awareness of symptom, but easily tolerated
- **Moderate** is definitely acting like something is wrong
- **Severe** is extremely distressed or unable to do usually activities

EXAMPLES FOR MEASURING THE SIZE OF REACTIONS:

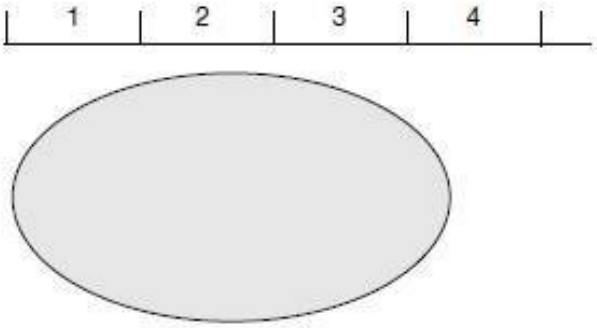
Example A: This reaction falls in the area marked 1 at its largest, so you would check the box marked "1."



Example B: This reaction falls in the area marked 3 at its largest, so you would check the box marked "3."



Example C: This reaction falls in the area marked 4 at its largest, so you would check the box marked "Over 3" and write in a 4.



C. Pediatric Vaccination Report Card (Less than 3 Years of Age)

Swelling and Redness

Estimate the size of the reaction at its largest from edge to edge. Use the VRC-provided ruler marks along the bottom of the page

Mark the box that best describes the size of the reaction:

- **1** if the greatest width is anywhere in the area marked 1 (**Example A**)
- **2** if the greatest width is anywhere in the area marked 2
- **3** if the greatest width is anywhere in the area marked 3 (**Example B**)
- **Over 3** if the greatest width is in any area marked with a number over 3. Write in the number (**Example C**)
- If the reaction is wider than the area marked 7, write in 8.

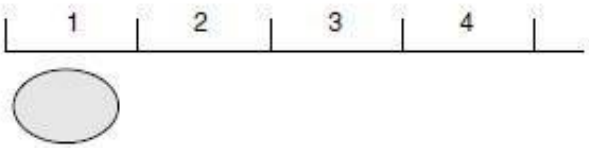
Pain or Tenderness or Other Reactions

Mark the box that best describes the severity of the reaction using the following definitions:

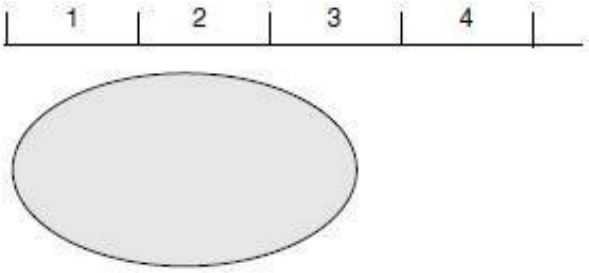
- **Mild** is awareness of symptom, but easily tolerated
- **Moderate** is definitely acting like something is wrong
- **Severe** is extremely distressed or unable to do usually activities

EXAMPLES FOR MEASURING THE SIZE OF REACTIONS:

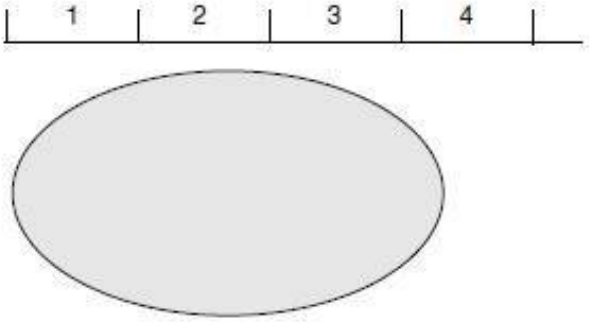
Example A: This reaction falls in the area marked 1 at its largest, so you would check the box marked "1."



Example B: This reaction falls in the area marked 3 at its largest, so you would check the box marked "3."



Example C: This reaction falls in the area marked 4 at its largest, so you would check the box marked "Over 3" and write in a 4.



10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

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 intervention, 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.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c,d] • Intrauterine hormone-releasing system (IUS)[c,e] • IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[e]
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. [e] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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.[1]

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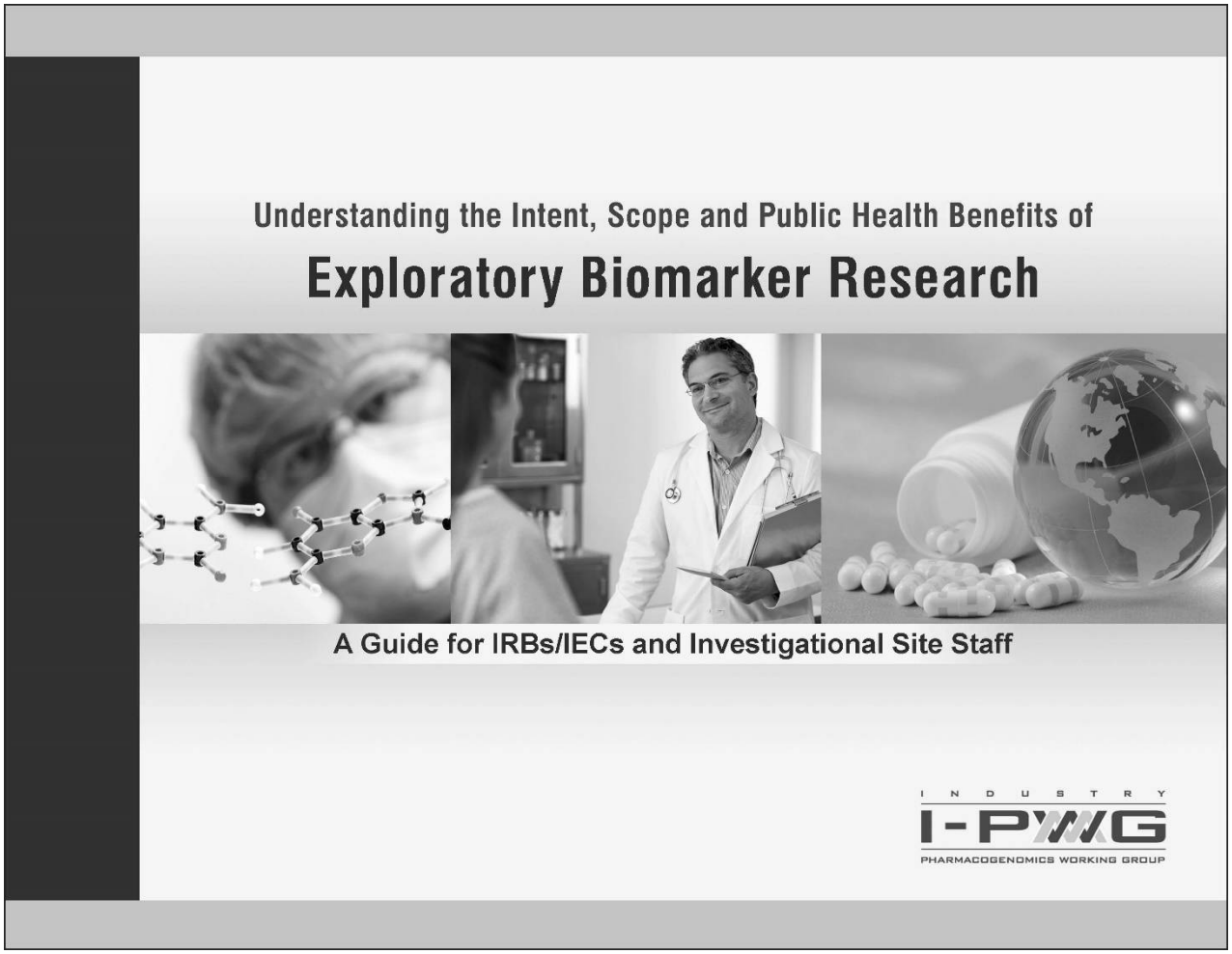
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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

10.6.1 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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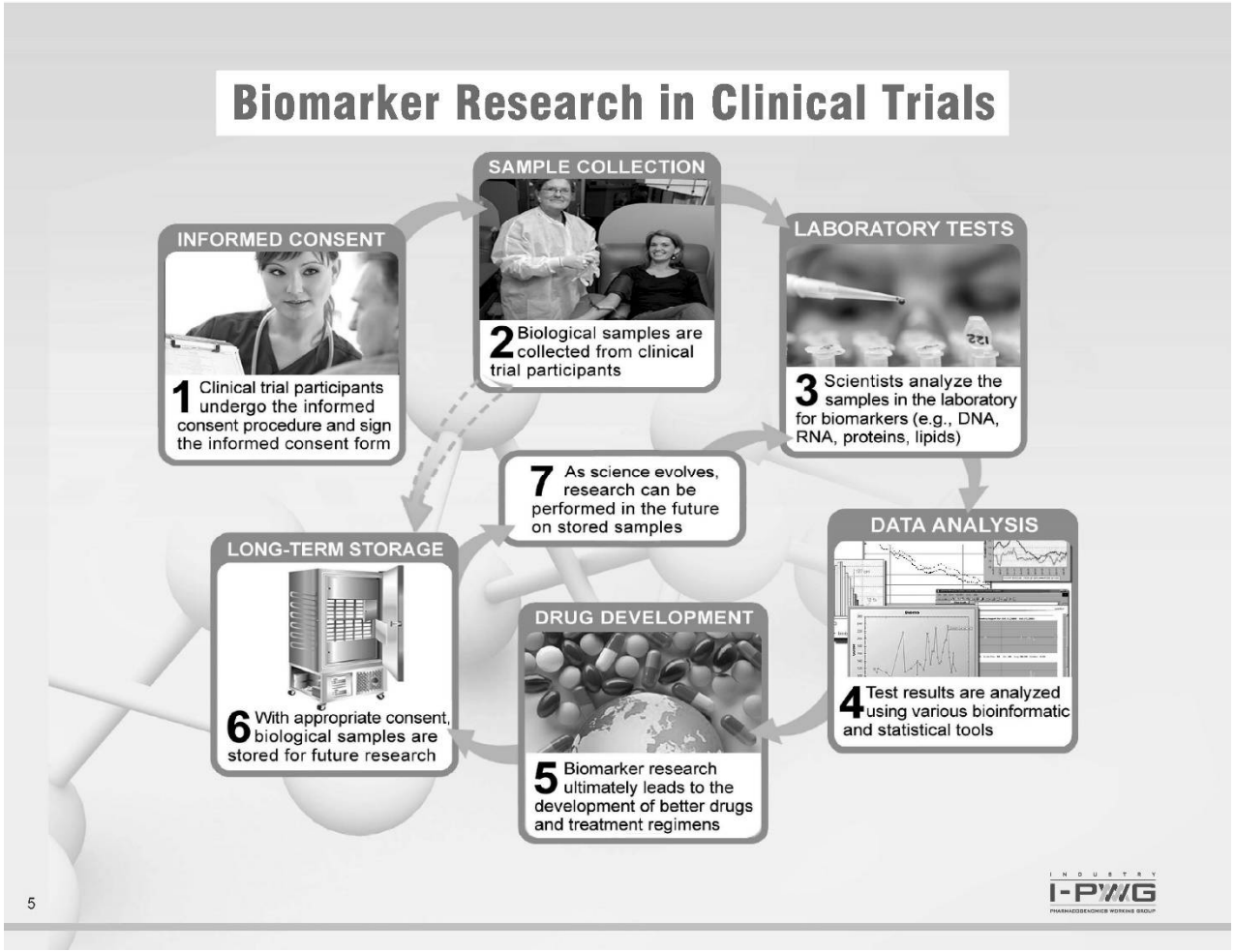
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al.* 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: **www.i-pwg.org**.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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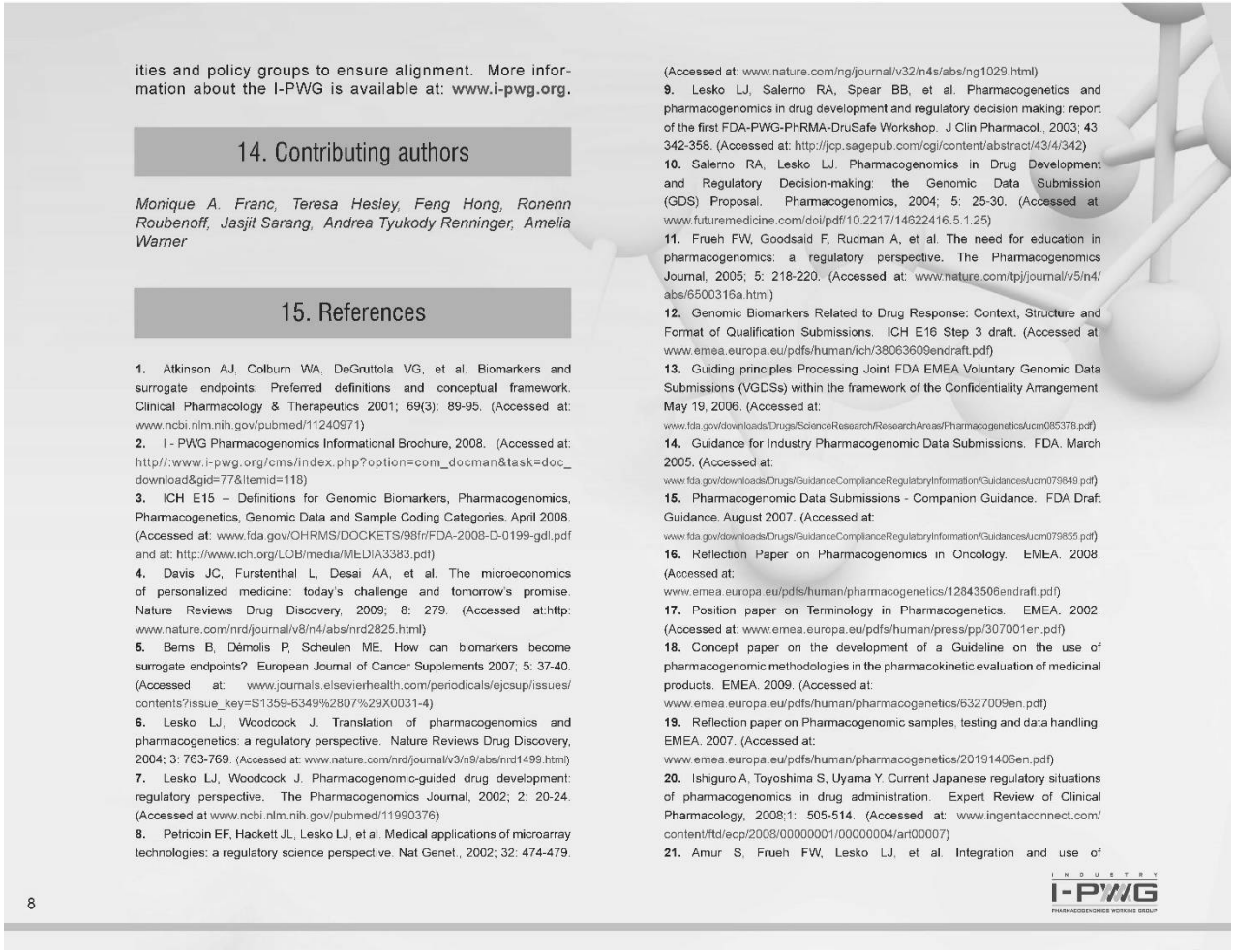

ities and policy groups to ensure alignment. More information about the I-PWG is available at: **www.i-pwg.org.**

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All-Participants-as-Treated
b-hCG	beta human chorionic gonadotropin
CBC	complete blood count
CI	confidence interval
CID	Component identification numbers
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DNA	deoxyribonucleic acid
DOD	delta optical density
DTaP	Diphtheria, Tetanus and Acellular Pertussis
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FBR	future biomedical research
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
gp	glycoprotein
gpELISA	glycoprotein antigen-based enzyme-linked immunosorbent assay
Hib	Haemophilus influenzae type b
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
IPV	inactivated poliovirus
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MRC-5	Medical Research Council cell strain 5
MSD	Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
OD	optical density
PD	postdose
PFU	plaque forming units
PGt	pharmacogenetic
PK	pharmacokinetic

Abbreviation	Expanded Term
PP	Per-protocol
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TCC	tissue culture control
OD	optical density
US	United States
VRC	Vaccination Report Card
VZV	varicella-zoster virus
WOCBP	woman/women of childbearing potential

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