Official Protocol Title:	A Phase 3, Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX™ Passage Extension 34 (PE34) Process Administered Concomitantly with M-M-R™ II
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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase 3, Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX™ Passage Extension 34 (PE34) Process Administered Concomitantly with M-M-R™ II

IND NUMBER: 0375
EudraCT NUMBER: Not applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.2.2.1	Serious Adverse Events	Updated that serious adverse events (SAEs) should be reported from the time period beginning at treatment allocation/randomization through 6 months (~180 days) following the second vaccination (instead of through 14 days [42 days for live attenuated vaccines] after each vaccination).	The reporting period of SAEs has been amended to remain consistent with the reporting standards within the VARIVAX™ program.
4.2.3.2	Safety Endpoints	Added unsolicited injection-site reactions from the eVRC, occurring on Days 1 through 42 after each vaccination as a safety parameter for the trial.	This section has been amended to clarify that unsolicited injection-site reactions occurring on Days 1 through 42 are collected as a safety parameter for the trial. As detailed in the previously issued Protocol Clarification Letter, unsolicited injection-site reactions were always intended to be collected in this trial; however, the previous version of the protocol did not list unsolicited injection-site reactions in this section of the protocol. This change provides consistency within the protocol.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.2.1.2	Administration of Trial Vaccines	Removed the requirement that all used and unused vaccine vials should be returned to the Sponsor upon completion of the trial.	This change is being made to allow sites to dispose of used vaccine vials at sites that have appropriate standards and processes in place.
6.0 7.1.2.1.4	Trial Flow Chart Temperature Procedures	Clarified that parents/legally acceptable representative should not record oral or otic temperatures.	This change is being made to provide clarity regarding the methodology of temperature assessment by parents/legally acceptable representatives.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Immunogenicity and Safety of VARIVAX™ Passage Extension 34 (PE34) Process in Children
Sponsor Product Identifiers	V210 Varicella virus vaccine live (Oka/Merck)
Trial Phase	Phase 3
Clinical Indication	Active immunization for the prevention of varicella in individuals 12 months of age and older
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Subcutaneous
Trial Blinding	Double-blind
Vaccination Groups	Healthy children who are 12 to 23 months of age will be randomized to receive 2 doses of either VARIVAX™ Passage Extension 34 (PE34) process (Group 1) or VARIVAX™ (2016 commercial product) (Group 2), each given approximately 3 months apart, concomitantly with M-M-R™ II
Number of trial subjects	Approximately 600 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 18 months from the time that written informed consent is provided for the first subject until the last subject's last study-related phone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result.
Duration of Participation	Each subject will participate in the trial for approximately 9 months from the time the subject/legally acceptable representative signs the informed consent form through the final contact.
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, comparator-controlled, multicenter, double-blind trial to evaluate the safety, tolerability, and immunogenicity of the VARIVAX™ (varicella virus vaccine live, Oka/Merck; V210, Merck) Passage Extension 34 (PE34) process compared with the VARIVAX™ (2016 commercial product) in healthy children who are between 12 to 23 months of age.

Approximately 600 subjects will be enrolled. Subjects will be randomized into 1 of 2 vaccination groups (ratio 1:1) with approximately 300 subjects per group. Group 1 will receive 2 doses of VARIVAX™ PE34 process, given concomitantly with M-M-R™ II [measles, mumps, and rubella virus vaccine live, Merck], approximately 3 months apart.

Group 2 will receive 2 doses of VARIVAX™ (2016 commercial product), given concomitantly with M-M-R™ II, approximately 3 months apart.

The enrollment period for the trial is expected to be approximately 9 months. Once enrolled, the total duration of the trial for a subject (from first visit to last contact) will be approximately 9 months. A subject is considered to have completed the trial when (1) both scheduled trial vaccinations are received, (2) both blood samples have been collected, and (3) the 42-day safety data after each vaccination have been collected. A subject is considered to have completed the extended safety follow-up when the last protocol-specified phone call is completed, and all safety data have been collected.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

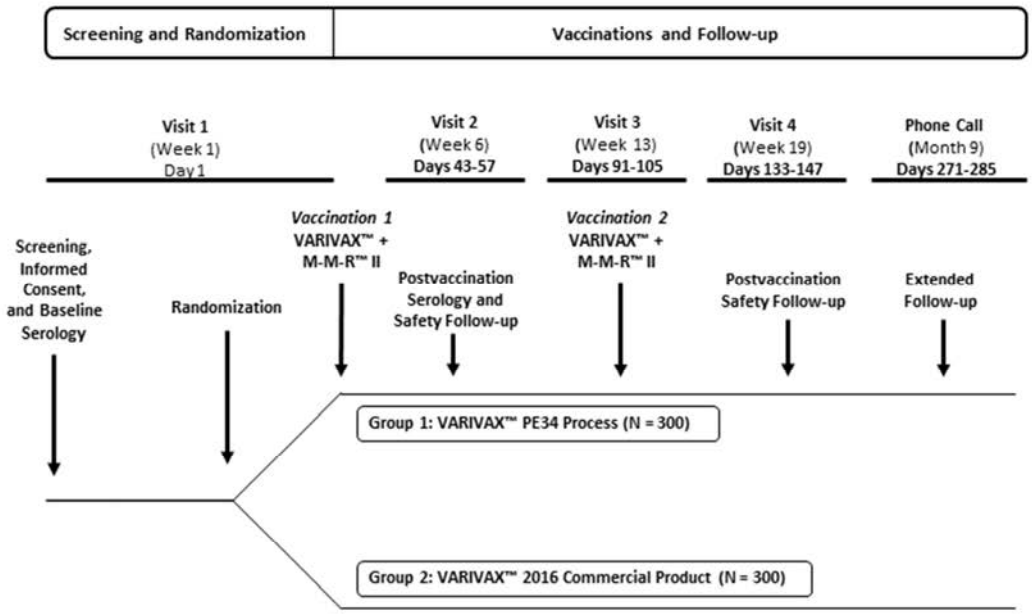

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

The following objectives will be evaluated in healthy children aged 12 to 23 months.

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To demonstrate that a single dose of VARIVAX™ PE34 process induces varicella-zoster virus (VZV) antibody responses 6 weeks Postvaccination 1 that are noninferior to those induced by VARIVAX™ 2016 commercial product.

   The primary endpoints for measuring the VZV antibody responses are the response rate and the geometric mean titer (GMT). The response rate is defined as the proportion of subjects with VZV antibody titer ≥5 glycoprotein enzyme-linked immunosorbent assay (gpELISA) units/mL 6 weeks Postvaccination 1 among subjects who were seronegative to VZV (titers <1.25 gpELISA units/mL) at baseline.

   Hypotheses:

   (1) Six weeks Postvaccination 1, VARIVAX™ PE34 process induces VZV antibody responses that are noninferior to those induced by VARIVAX™ (2016 commercial product), as measured by the response rate.

   (The statistical criterion for noninferiority of the response rate corresponds to the lower bound of the 2-sided 95% confidence interval [CI] on the difference in response rates [VARIVAX™ PE34 process minus VARIVAX™ 2016 commercial product] excluding a decrease of 10 percentage points or more.)

   (2) Six weeks Postvaccination 1, VARIVAX™ PE34 process induces VZV antibody responses that are noninferior to those induced by VARIVAX™ (2016 commercial product), as measured by the GMT.

   (The statistical criterion for noninferiority of the GMT corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio [VARIVAX™ PE34 process/VARIVAX™ 2016 commercial product] being >0.67.)

2) **Objective:** To demonstrate that a single dose of VARIVAX™ PE34 process induces an acceptable VZV antibody response 6 weeks Postvaccination 1.

   Hypothesis:

   (3) Six weeks Postvaccination 1, VARIVAX™ PE34 process induces an acceptable VZV antibody response, as measured by the response rate.

   (The statistical criterion for an acceptable antibody response corresponds to the lower bound of the 95% CI for the response rate to VZV in the group receiving VARIVAX™ PE34 process being >76.0%.)

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective:** To assess the safety and tolerability of the first and second doses of VARIVAX™ PE34 process.

2) **Objective**: To summarize the VZV antibody responses after a single dose of VARIVAX™ PE34 process and after a single dose of VARIVAX™ (2016 commercial product). The VZV immunogenicity data will be summarized for the antibody response rates, seroconversion rates and GMTs, along with the associated 95% CI for these parameters. No formal testing will be conducted.

Success for the trial requires success on the 3 hypotheses based on the primary objectives.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the package insert and Investigator's Brochure for detailed background information on VARIVAX™.

4.1.1 Pharmaceutical and Therapeutic Background

Varicella is a generalized illness that has an incubation period of about 12 to 16 days and is highly contagious. It is characterized by a papulovesicular rash that 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 after varicella infection is generally long-lasting, the virus may persist in latent form in the peripheral nerve tissue (ganglia). Herpes zoster ([HZ] or shingles) may develop as a result of the reactivation of latent VZV.

VARIVAX™ is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.

Before the introduction of a varicella vaccine (VARIVAX™), an estimated 4 million cases of varicella occurred annually in the United States [1], resulting in 10,000 hospitalizations and over 100 deaths [2] [3]. VARIVAX™ was licensed in 1995 after studies 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 [4]. Following licensure, vaccine coverage has increased to an estimated 90% of the pediatric population in the United States [5] [6], thereby reducing varicella incidence by up to 91% [5] and varicella-related hospitalizations by 75% to 88% [7] [8]. During the first 12 years after licensure of VARIVAX™ in the United States, varicella-related mortality decreased by 88%, including a 97% reduction in individuals younger than 20 years of age, and a 96% reduction in individuals younger than 50 years of age [9]. Recent epidemiologic studies have demonstrated that VARIVAX™ affords long-term protection over 14 years against varicella and also imparts herd immunity to unvaccinated individuals in settings where vaccine adoption is widespread [10]. Currently,

the Advisory Committee on Immunization Practices (ACIP) in the United States recommends (as of 2006) that a 2-dose regimen be administered in childhood [11].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Following the recommendation of a 2-dose varicella vaccination schedule by the ACIP, and the approval of other VZV-containing products (ZOSTAVAX™ [zoster vaccine live, Merck] and ProQuad™ [measles, mumps, rubella, and varicella virus vaccine live, Merck]), the demand for VZV-containing vaccines has increased.

The VARIVAX™ PE34 process will extend the availability of VZV (Oka/Merck)-containing vaccines and is not expected to change the safety profile or effectiveness of the vaccine.

The purpose of this Phase 3, randomized, double-blind, multicenter, controlled trial is to assess the immunogenicity, safety, and tolerability of VARIVAX™ PE34 process in comparison with VARIVAX™ (2016 commercial product).

VARIVAX™ is indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.

This trial will be performed in healthy children who are between 12 to 23 months of age, which is the recommended age group for the first dose of VZV-containing vaccine.

4.2.2 Rationale for Dose Selection/Regimen

Both VARIVAX™ PE34 process and VARIVAX™ (2016 commercial product) are administered subcutaneously as a 0.5-mL dose. The dose of VARIVAX™ PE34 process is the same as for VARIVAX™ (2016 commercial product) because VARIVAX™ PE34 is formulated in such a way to contain the same minimum potency at the time of release.

All subjects enrolled in this trial will receive 2 doses of trial vaccine administered concomitantly with M-M-R™ II. This is consistent with the recommended regimens in the United States and European Union (EU). In the United States, the ACIP recommends a 2-dose regimen of varicella vaccines. A minimum interval of 3 months (90 days) is recommended between each dose of VZV-containing vaccines when administered to children. In the EU, at least 1 month must elapse between the first and second dose of any live viral attenuated vaccine. In both the United States and the EU, varicella vaccine can be administered to children as a 2-dose series. In regions where vaccination of toddlers against varicella is the standard of care, VZV-containing vaccines are typically administered concurrently with measles-mumps-rubella-containing vaccines.

4.2.3 Rationale for Endpoints

4.2.3.1 Immunogenicity Endpoints

The immunogenicity endpoints for this trial are consistent with those used in previous clinical studies of VARIVAX™. The primary time point for the assessment of immunogenicity analyses will be at 6 weeks Postvaccination 1.

The presence of VZV-specific antibodies will be assessed by gpELISA. The gpELISA will be used to detect antibody (immunoglobulin G [IgG]) to VZV pre- and postvaccination with VZV-containing vaccines. The gpELISA assay is the primary assay used by the Sponsor to evaluate the serologic response to VZV vaccines; the performance characteristics of this assay have been well established in previous clinical trials. The response rate for VZV is defined as the proportion of subjects with a postvaccination VZV antibody titer ≥5 gpELISA units/mL for subjects who were seronegative to VZV (titer <1.25 gpELISA units/mL) at baseline. An antibody titer ≥5 gpELISA units/mL correlates with long-term protection [12].

4.2.3.2 Safety Endpoints

Throughout the clinical development program VARIVAX™ has demonstrated an acceptable safety profile in children. Moreover, across dose ranges and manufacturing processes, aggregate safety data from the varicella clinical development program demonstrate the consistency of the safety profile of VARIVAX™, with similar rates of local and systemic adverse experiences and temperature data. Additionally, in clinical studies that have evaluated the concomitant administration of VARIVAX™ with M-M-R™ II, concomitant use did not adversely affect the safety profile of either vaccine.

In clinical studies using a 2-dose regimen of VZV-containing vaccine in children, the incidence of injection-site reactions after vaccination was generally higher Postvaccination 2 than Postvaccination 1, although the injection-site reactions were short in duration and mild in intensity and size; whereas, significantly lower incidences of elevated temperatures and noninjection-site varicella-like rashes were observed Postvaccination 2 compared with Postvaccination 1.

As with previous VARIVAX™ studies, the postvaccination safety follow-up period will be 42 days after each vaccination. The safety parameters for this trial will include the proportion of subjects with the following:

1) elevated temperatures ≥102.2°F [≥39.0°C] oral equivalent) up to 42 days after each trial vaccination;
2) varicella-like, zoster-like, measles-like, or rubella-like rashes or mumps-like symptoms occurring up to 42 days after each trial vaccination;
3) solicited injection-site reactions (using the electronic vaccination report card [eVRC]), such as redness, swelling, and pain/tenderness/soreness, occurring within 5 days after each trial vaccination;

4) all unsolicited injection-site reactions occurring on Days 1 through 42 after each trial vaccination;
5) systemic adverse experiences up to 42 days after each trial vaccination;
6) serious adverse experiences throughout the trial duration; and
7) medically attended adverse events from Day 133 through Day 271.

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (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 trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects in this trial are expected to receive the same benefit, as established with VARIVAX™ and M-M-R™ II. The change in production process is not expected to affect the benefit/risk ratio.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying VARIVAX™ package insert and Investigator's Brochure, M-M-R™ II package insert, and informed consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy children who are between 12 and 23 months of age (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be between 12 to 23 months of age upon receipt of the first trial vaccination (subject is able to enroll up to 1 day before 24 months of age).
2. Be in good health based on medical history.
3. Have a negative clinical history for varicella, HZ, measles, mumps, and rubella.
4. Be able to complete all scheduled visits and comply with the trial procedures.
5. Have a parent/legally acceptable representative who understands the trial procedures, alternate treatments available, and risks involved with the trial and voluntarily agree to participate in the trial by providing written informed consent.
6. Have a parent/legally acceptable representative who is able to read, understand, and complete the eVRC.
7. Have a parent/legally acceptable representative who also acknowledges that he or she:
    a. will attend all scheduled visits
    b. will comply with the trial procedures, and
    c. will have access to a telephone and be willing to complete the safety follow-up phone call.
8. The subject's parent/legally acceptable representative may also provide written informed consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

*If the subject meets any of the exclusion criteria marked with an asterisk (*), the Day 1 visit may be rescheduled for a time when these exclusion criteria are no longer met; however, the subject would only be permitted to continue with a delayed vaccination if the visit can be performed within 7 days of consent.

1. Has received any measles-, mumps-, rubella-, or VZV-containing vaccine, either alone or in any combination, at any time before the trial, or is anticipated to receive any of these vaccines, either alone or in any combination, during the trial.

2. Has any congenital or acquired immune deficiency, neoplastic disease, or depressed immunity, including those resulting from corticosteroid use (see Exclusion Criterion #3 and Section 5.5 – Concomitant Medications) or other immunosuppressive therapy.
3. Has received 1) systemic immunomodulatory steroids (no more than the equivalent of 2 mg/kg total daily dose of prednisone or >20 mg/day of prednisone or equivalent for subjects weighing >10 kg) for more than 7 consecutive days within 3 months before entering trial, or 2) any dose of systemic immunomodulatory steroids within 7 days before entering trial, or 3) is expected to require systemic immunomodulatory steroids during the course of the trial.

   Exception: Subjects who require nonsystemic steroids (e.g., topical, ophthalmic, inhaled) will be eligible for vaccination.
4. Has any blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
5. Has a history of allergy or anaphylactic reaction to neomycin, gelatin, sorbitol, egg proteins (egg or egg products), chicken proteins, or any component of VARIVAX™ or M-M-R™ II, as stated in the package inserts.
6. *Has received salicylates (e.g., aspirin or any aspirin-containing products) within 14 days before vaccination.
7. *Has had an exposure to varicella, HZ, measles, mumps, or rubella in the last 4 weeks before trial vaccination involving:
   a. Continuous household contact, or
   b. Playmate contact (generally >1 hour of indoor play), or
   c. 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
   d. Contact with a newborn whose mother had an onset of chickenpox within ≤5 days before delivery or within 48 hours after delivery.
8. *Was vaccinated with a licensed, inactivated (nonlive) vaccine (e.g., inactivated poliovirus [IPV], Diphtheria, Tetanus, and Acellular Pertussis [DTaP], *Haemophilus influenzae* type b [Hib]) within 14 days or less before any dose of the trial vaccines or is expected to be vaccinated during the 42-day safety follow-up period after each trial vaccination.
9. *Was vaccinated with any licensed live vaccine within ≤30 days before any dose of the trial vaccines or is expected to be vaccinated within the 42-day safety follow-up period after each trial vaccination.

10. *Has had a recent (within 72 hours) history of febrile illness (≥102.2°F [39.0°C] oral equivalent) before the trial vaccination. Temperature may be converted to oral equivalent by adding 1.0°F to axillary temperatures and subtracting 1.0°F from rectal temperatures.
11. Has received immunoglobulin, a blood transfusion, or blood-derived products (does not include autologous blood/blood products) within 5 months before vaccination or plans to receive these products while enrolled in this trial.
12. Has a history of seizure disorder, including single febrile seizure.
13. Has a history of thrombocytopenia.
14. Was born to a human immunodeficiency virus (HIV)-infected mother.
15. Has a diagnosis of active untreated tuberculosis.
16. Is currently participating in (30 days or less before enrollment) or scheduled to participate in any other clinical trial other than a surveillance trial during the planned trial period for this trial.
17. Has any other underlying medical condition that, in the opinion of the investigator, may interfere with the evaluation of trial objectives.
18. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

5.1.3.1 Subject Deferment Criteria (Before Vaccination 2)

These subject deferment criteria must be reviewed for each subject before Vaccination 2 to ensure that none of the criteria apply to the subject, and/or that Vaccination 2 is deferred for the subject for an appropriate period of time. The subject would only be permitted to continue with a delayed vaccination if the visit can be performed within the allowed window.

The subject should be deferred from continuing in the trial if the subject:

19. Has had exposure to varicella or HZ Postvaccination 1 (defer Vaccination 2 until 4 weeks after the exposure):
    a. Continuous household contact, or
    b. Playmate contact (generally >1 hour of indoor play), or
    c. Hospital contact (in same 2- to 4-bed room or adjacent beds in a large ward or prolonged face-to-face contact with an infectious staff member or patient), or
    d. Contact with a newborn whose mother had onset of chickenpox within ≤5 days before delivery or within 48 hours after delivery.
20. Has had exposure to measles, mumps, or rubella since Vaccination 1 (defer Vaccination 2 until 4 weeks after exposure).

21. Has had recent (within 72 hours) history of febrile illness (≥102.2°F [39.0°C] oral equivalent) before the trial vaccination (defer Vaccination 2 until >72 hours after resolution of febrile illness). Temperature may be converted to oral equivalent by adding 1.0°F to axillary temperatures and subtracting 1.0°F from rectal temperatures.

22. Has received any dose of systemic immunomodulatory steroids within 7 days before Vaccination 2 (defer Vaccination 2 until a minimum of 7 days after systemic immunomodulatory steroids).

23. Has had any licensed inactivated vaccine administered since Vaccination 1 (defer Vaccination 2 until a minimum of 15 days after nontrial vaccination[s]).

24. Has had any licensed live vaccine administered since Vaccination 1 (defer Vaccination 2 until a minimum of 31 days after nontrial vaccination[s]).

25. Has had receipt of salicylates (e.g., aspirin or any aspirin-containing products) since Vaccination 1 (defer Vaccination 2 until 14 days after taking medication).

26. Has had any medical condition that, in the opinion of the investigator, may interfere with the evaluation of the trial objectives. (The amount of time Vaccination 2 is deferred will be determined by the investigator.)

5.1.3.2 Criteria for Excluding Subjects from Receiving Vaccination 2

These subject exclusion criteria must be reviewed for each subject before Vaccination 2 to ensure that none of the criteria apply to the subject.

The subject must be excluded from receiving Vaccination 2 if the subject:

27. Has had any immunoglobulin, nonautologous blood, or blood products administered Postvaccination 1.

28. Has had any nontrial measles-, mumps-, rubella-, or VZV-containing vaccine administered Postvaccination 1.

29. Has received systemic immunomodulatory steroids (no more than the equivalent of >2 mg/kg total daily dose of prednisone or equivalent or >20 mg/day of prednisone or equivalent for subjects weighing >10 kg) for more than 7 consecutive days Postvaccination 1.

30. Has any blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems diagnosed Postvaccination 1.

31. Has had any acquired or congenital immunodeficiency or active tuberculosis diagnosed Postvaccination 1.

32. Has had the occurrence of varicella infection Postvaccination 1.

33. Has had a vaccine-related allergic or anaphylactoid reaction reported Postvaccination 1.

34. Has enrolled in any other clinical trial other than a surveillance trial Postvaccination 1.

35. Has had a seizure, including a febrile seizure, Postvaccination 1.

36. Has had thrombocytopenia Postvaccination 1.

5.2 Trial Vaccination(s)

The vaccines to be used in this trial are outlined below in Table 1.

Table 1 Trial Vaccinations

Vaccine	Dose/Potency	Dose Frequency	Route of Administration	Vaccination Regimen	Use
VARIVAX™ PE34 process (Group 1)	0.5 mL after reconstitution	2 doses; 3 months between each dose	Subcutaneous injection	Visit 1 (Day 1) and Visit 3 (Week 13 [Days 91-105])	Investigational
VARIVAX™ (2016 commercial product) (Group 2)	0.5 mL after reconstitution	2 doses; 3 months between each dose	Subcutaneous injection	Visit 1 (Day 1) and Visit 3 (Week 13 [Days 91-105])	Standard of care
M-M-R™ II (Groups 1 and 2)	0.5 mL after reconstitution	2 doses; 3 months between each dose	Subcutaneous injection	Visit 1 (Day 1) and Visit 3 (Week 13 [Days 91-105])	Standard of care

Vials of vaccine will be labeled with component identification numbers (CIDs). Care should be taken to ensure that each subject receives the appropriate clinical materials labeled with their specific CID.

Trial vaccinations are given on the day of randomization or as close as possible to the date on which the subject is allocated/assigned. All supplies indicated in Table 1 above will be provided centrally 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

Subjects will be randomized to 1 of 2 vaccination groups to receive either two 0.5-mL subcutaneous doses of VARIVAX™ PE34 process (Group 1) or two 0.5-mL subcutaneous doses of VARIVAX™ (2016 commercial product) (Group 2) approximately 3 months apart. Dose 1 will be administered at Visit 1 on Day 1 of the trial, and Dose 2 will be administered at Visit 3 (Week 13 [Days 91-105]). Each dose of VARIVAX™ PE34 process and VARIVAX™ (2016 commercial product) will be administered concomitantly with M-M-R™ II.

5.2.3 Trial Blinding

A double-blinding technique with in-house blinding will be used. VARIVAX™ PE34 process and VARIVAX™ (2016 commercial product) will be packaged identically so that the blind is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the vaccine administration or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Vaccine Allocation

Vaccine randomization will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). There are 2 vaccination groups. Subjects will be assigned randomly in a 1:1 ratio to VARIVAX™ PE34 process (Group 1) or VARIVAX™ (2016 commercial product) (Group 2), respectively.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination 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 subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject’s legally acceptable representative.

All medications administered from 30 days before each trial vaccination through 42 days after each trial vaccination should be recorded on the appropriate eCRF. Subjects should not have received any previous measles-, mumps-, rubella-, or VZV-containing vaccines, either alone or in any combination, or any such vaccines outside of trial protocol for the duration of the trial.

Subjects should not have received salicylates (e.g., aspirin or any aspirin-containing products) during the 14 days before Vaccination 1, and should not receive these products until after 42 days after Vaccination 2, because the use of salicylates in children with varicella has been associated with Reye syndrome. Subjects must not have received any immunoglobulin, a blood transfusion, or blood-derived products (does not include autologous blood/blood products) for at least 5 months (150 days) before vaccination and should not receive these products while enrolled in this trial, unless there is a medical necessity warranting their use.

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

1. Use of topical, ophthalmic, and inhaled steroids is permitted.
2. Use of systemic immunomodulatory steroids must meet the following criteria:
    - Subjects should not receive any dose of systemic immunomodulatory steroids within 7 days before or after each vaccination.
    - Subjects should not receive systemic immunomodulatory steroids (no more than the equivalent of 2 mg/kg total daily dose of prednisone or equivalent or >20mg/day of prednisone or equivalent for subjects weighing >10 kg) for more than 7 consecutive days from the time of trial start through the end of the 42-day safety follow-up period Postvaccination 2.

If higher doses of systemic immunomodulatory steroids or other systemic immunosuppressive agents are administered after trial entry but before Vaccination 2, or if the subject otherwise develops an immunosuppressive condition in this interval, then the second dose of trial vaccines should be discontinued.

It is preferable that other vaccines routinely administered to children who are between 12 months to 23 months of age be given outside of the trial period so as not to confound the results from this trial. These vaccines will not be provided by the Sponsor or Sponsor designee. If necessary, enrollment in the trial can be deferred if a medically important vaccine needs to be administered; however, the subject would only be permitted to continue with a delayed vaccination if the visit can be performed within the allowed window. A full 15 days must elapse between the receipt of inactivated nontrial vaccines and enrollment into the trial. A full 31 days must elapse between the receipt of live nontrial vaccines (e.g., yellow fever) and enrollment into the trial.

If medically necessary, both licensed inactivated and live nontrial vaccines may be administered in the interval between Visit 2 and Visit 3. As specified in Section 5.1.3, a minimum of 43 days should elapse between Visit 1 (when the first dose of trial vaccine is administered) and receipt of the inactivated or live nontrial vaccine. In addition:

- If a licensed, inactivated (**nonlive)** vaccine (e.g., IPV, DTaP, Hib) is given between Visits 2 and 3, the second dose of trial vaccine must not be given until at least 15 days have elapsed.
- If a licensed **live** vaccine is given between Visits 2 and 3, the second dose of trial vaccine must not be given until at least 31 days have elapsed.

After the successful completion of trial procedures at Visit 4 (Week 19 [Days 133-147 Postvaccination 1]), both inactivated and live nontrial vaccines may be administered.

5.6 Rescue Medications & Supportive Care

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

See Section 7.1.2.1.3, General Precautions for Administration, regarding administration of epinephrine in the event of an anaphylactic reaction.

5.7 Diet/Activity/Other Considerations

No special restrictions on diet or activity apply.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Vaccination

Discontinuation of vaccination does not represent withdrawal from the trial.

As certain data on clinical events beyond vaccination discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued vaccination. Therefore, all subjects who discontinue trial vaccination prior to completion of the vaccination period will still continue to participate in the trial as specified in Section 6.0 (Trial Flow Chart) and Section 7.1.5.3 (Discontinued Subjects Continuing to be Monitored in the Trial) unless consent is withdrawn. For subjects who will not receive Vaccination 2, all tasks except vaccination and eVRC should be completed.

Subjects may discontinue vaccination at any time for any reason or be dropped from vaccination at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from vaccination by the investigator or the Sponsor if vaccination is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at vaccination discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from vaccination but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue vaccination.
- The subject has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.
- The subject meets any of the criteria in Section 5.1.3.
- Treatment unblinding.

For subjects who are discontinued from vaccination but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, except vaccination and eVRC should be completed.

Discontinuation from vaccination is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart vaccination.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive vaccination or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who withdraws from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when written informed consent is provided for the first subject. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Visit Number:	1	2	3	4	5
Visit Title:	Randomization/ Vaccination 1	Vaccination 1 Follow-up[a]	Vaccination 2[b]	Vaccination 2 Follow-up[a,c]	Phone Call[c]
Trial Timing:	Week 1	Week 6	Week 13	Week 19	Month 9
Trial Days:	Day 1	Days 43-57	Days 91-105	Days 133-147	Days 271-285
Administrative Procedures					
Obtain informed consent	X				
Obtain informed consent for future biomedical research[d]	X				
Assign screening number	X				
Distribute subject identification card	X				
Review inclusion/exclusion criteria	X				
Review deferment/exclusion criteria (before Vaccination 2)			X		
Review medical history	X				
Review concomitant medication and nontrial vaccines	X	X	X	X	
Assign treatment allocation/randomization using IVRS/IWRS	X		X		
Laboratory Procedures/Assessments					
Obtain buccal swabs (DNA) for Future Biomedical Research[d]	X				
Obtain blood sample for immunogenicity testing[e]	X	X			
Clinical Procedures/Assessments					
Take temperature (oral or equivalent)[f]	X		X		
Administer VARIVAX™ (left arm [or left anterolateral thigh])[f] Group 1: VARIVAX™ PE34 process Group 2: VARIVAX™ (2016 commercial product)	X		X		
Administer M-M-R™ II (right arm [or right anterolateral thigh])[f]	X		X		
Observe subject for anaphylaxis or other allergic reaction (at least 30 minutes)	X		X		
Distribute eVRC/review instructions with subject/legally acceptable representative[g]	X		X		
Review eVRC reports with legally acceptable representative[h]		X		X	
Educate subject/legally acceptable representative on serious adverse events definition and reporting	X	X	X	X	
Review adverse events and serious adverse events[i]		X	X	X	
Collect eVRC device				X	
Active assessment (using scripted safety questions) for occurrence of possible serious adverse events and medically attended adverse events					X

a. Visit 2 and Visit 4 should be performed no sooner than 42 days after the previous vaccination.
b. The subject would only be permitted to continue with a delayed vaccination if the visit can be performed within the 14-day window.
c. For subjects who will not receive Vaccination 2, all tasks except vaccination and electronic Vaccination Report Card should be completed.
d. Informed consent for optional future biomedical research samples must be obtained to collect the DNA sample.

Visit Number:	1	2	3	4	5
Visit Title:	Randomization/ Vaccination 1	Vaccination 1 Follow-up[a]	Vaccination 2[b]	Vaccination 2 Follow-up[a,c]	Phone Call[c]
Trial Timing:	Week 1	Week 6	Week 13	Week 19	Month 9
Trial Days:	Day 1	Days 43-57	Days 91-105	Days 133-147	Days 271-285

e. A 3-mL blood sample will be taken on Day 1, immediately before vaccination with VARIVAX™ and at Week 6 (43-57 days after Day 1 vaccination with VARIVAX™. The Visit 1 (Day 1) immunogenicity blood sample is mandatory for enrollment. Leftover main trial serum will be stored for future biomedical research if the parent/legally acceptable representative consents to future biomedical research.

f. Before vaccination with trial vaccine, review all eligibility criteria, including subject's temperature. If the subject has a fever (defined as an oral temperature of ≥ 102.2°F (39.0°C) or equivalent, the subject should not receive trial vaccine and the vaccination visit should be rescheduled until >72 hours after resolution of the febrile illness. If the subject's axillary temperature is ≥98.6°F (37.0°C), the parent/legally acceptable representative will be requested to further measure and record the subject's rectal temperature in the eVRC. Parents/legally acceptable representatives should only record axillary temperatures and rectal temperatures as indicated. Oral temperatures and otic temperatures should not be recorded by parents/legally acceptable representatives.

g. The eVRC device is dispensed at Visit 1. Only instructions are reviewed at Visit 3.

h. The eVRC (Section 7.1.1.9) is required to be completed for a full 42 days after each vaccination. The eVRC device will be distributed at Visit 1 and returned to the site at Visit 4. At Visit 3, the subject or parent/legally acceptable representative must be reminded to return with the eVRC device at Visit 4.

i. The development of varicella-like, HZ-like, measles-like and rubella-like rashes and mumps-like symptoms through 42 days after vaccination will be recorded on the eVRC. The subject's parent/legally acceptable representative will be instructed to contact trial personnel immediately if a varicella- or HZ-like rash develops. Subjects are required to be seen at the clinic within 72 hours of the rash presentation. Trial personnel will review the completed eVRC reports to identify any unreported occurrences of these specific conditions.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject's legally acceptable representative. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

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

A copy of the signed and dated consent form should be given to the subject's legally acceptable representative before that subject's participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject's legally acceptable representative must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to willingness for the subject to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's legally acceptable representative's dated signature.

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject's legally acceptable representative, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject's legally acceptable representative.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

The legally acceptable representative for each subject will be given a Subject Identification Card identifying the subject as a participant in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the legally acceptable representative for each subject with the a Subject Identification Card immediately after written informed consent is provided. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

The eligibility of a subject will be assessed, and a medical history will be obtained to ensure that the subject satisfies the inclusion and exclusion criteria of the trial. No physical examination is required for entry into the trial.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

Before trial vaccination, the investigator or qualified designee will review and record prior medications and vaccinations received by the subject within the specified time periods. Prohibited prior medications and vaccinations are listed in the Exclusion Criteria in Section 5.1.3.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. Prohibited concomitant medications are listed in Section 5.5.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

7.1.1.8 Trial Compliance (Medication/Diet/Activity)

Trial vaccine will be administered by the investigator or qualified designee. No special restrictions on diet or activity apply.

7.1.1.9 Distribution of Electronic Vaccination Report Card (eVRC)

The eVRC for this trial was developed to be provided electronically via a hand-held device. This item was structured as recommended in the final Food and Drug Administration (FDA) Patient Reported Outcome (PRO) Guidance. The investigator or delegate will train the subject/parent or legally acceptable representative in the use of the eVRC device before dispensing it to the subject/parent or legally acceptable representative at Visit 1 and will also review the instructions for using the eVRC device with the subject/parent or legally acceptable representative at Visit 3. At Visit 3, the subject/parent or legally acceptable representative must be reminded to return with the eVRC device at Visit 4. Specific injection-site reactions will be solicited from Day 1 through Day 5 after vaccination with the trial vaccine (VARIVAX™ PE34 or VARIVAX™ 2016 commercial product) and M-M-R™ II. Daily temperatures will be recorded on the eVRC from Day 1 through Day 42 after vaccination. If the subject's axillary temperature is ≥98.6°F (37.0°C), the parent/legally acceptable representative will be requested to further measure and record the subject's rectal temperature in the eVRC. The investigator or delegate will review the data captured on the eVRC with the subject at Visit 2 and Visit 4 and enter the data into the appropriate eCRF.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Vaccine Administration

7.1.2.1.1 Preparation of Trial Vaccine

The designated study site personnel will reconstitute the trial 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 sterile syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently swirl to mix thoroughly. Withdraw and administer the entire contents (~0.5 mL) of the vial.

CAUTION:

- Sterile syringes should be free of preservatives, antiseptics, and detergents as these substances may inactivate the vaccine virus.
- 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.
- Do not freeze reconstituted vaccine.

7.1.2.1.2 Administration of Trial Vaccines

VARIVAX™ should be administered subcutaneously in the outer aspect of the **upper left arm (deltoid) or left anterolateral thigh**. All vaccinations and location of injection should be recorded on the appropriate eCRF. A 25-gauge, 5/8" needle is recommended. Subjects should be observed for anaphylaxis or other reactions for at least 30 minutes after vaccination.

M-M-R™ II should be administered subcutaneously in the outer aspect of the **upper right arm (deltoid) or right anterolateral thigh**. All vaccinations and location of injection should be recorded on the appropriate eCRF. A 25-gauge, 5/8" needle is recommended. Subjects should be observed for anaphylaxis or other reactions for at least 30 minutes after vaccination.

Details of the vaccination should be documented, 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. If not **used within 30 minutes of removal from the refrigerator**, a new vial must be reconstituted. Do not freeze reconstituted vaccine. Vials that are reconstituted and not used must be recorded on the vaccine accountability form for this trial.

7.1.2.1.3 General Precaution for Administration of Vaccine

Adequate treatment provision, including epinephrine, should be available for immediate use should an anaphylactic reaction occur. Subjects should be observed for anaphylaxis or other reactions for at least 30 minutes after vaccination.

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

7.1.2.1.4 Temperature Procedures

The parent/legally acceptable representative for each subject will be instructed to measure and record in the eVRC the subject's axillary temperature 4 to 6 hours postvaccination and then daily, preferably at the same time each day, through 42 days after each vaccination. If the subject's axillary temperature is ≥98.6°F (37.0°C), the parent/legally acceptable representative will be requested to further measure and record the subject's rectal temperature in the eVRC. Trial personnel should advise the parent/legally acceptable representative on the proper manner in which to measure axillary and rectal temperatures to ensure that accurate measurements are obtained. The parents/legally acceptable representative should not record oral or otic temperatures.

7.1.2.1.5 Clinical Follow-up

Subjects will be followed for adverse events through 42 days after each vaccination. Specific injection-site reactions will be solicited from Day 1 through Day 5 after vaccination with the trial vaccine (VARIVAX™ PE34 or VARIVAX™ 2016 commercial product) and M-M-R™ II. Daily temperatures will be recorded on an eVRC from Day 1 through Day 42 after vaccination. Regardless of severity or causality, all unsolicited injection-site reactions; and all systemic adverse events, including varicella-, zoster-, measles-, rubella-like rashes and mumps-like symptoms, will be recorded on an eVRC for Day 1 through Day 42 after vaccination. Serious adverse events, including death, will be reported from Day 1 after the first dose of trial vaccine through Day 180 after the second dose of trial vaccine. Medically attended adverse events will be reported from Day 133 through Day 271. During the phone call at Day 271 (Day 180 Postvaccination 2), a scripted questionnaire will be used to determine if any serious adverse events or medically attended adverse events have occurred for each subject since completing the 42-day safety follow-up period Postvaccination 2.

The parent/legally acceptable representative of each subject will record the safety data on the eVRC and return the eVRC to the trial site at Visit 4. Trial personnel will review the eVRC for completeness, accuracy, and clarity. All information will be accurately recorded on the appropriate eCRFs.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pretrial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject, can be found in Section 12.3.

7.1.3.1 Laboratory Immunogenicity Evaluations

7.1.3.1.1 Blood Sample Collection for Antibody Measurement

A 3-mL blood sample will be obtained from all subjects just before vaccination at Visit 1 (Day 1) and at Visit 2 (Day 43 [+14 days] Postvaccination 1). For all subjects at Visit 1 (Day 1), it is mandatory to collect a blood sample before a subject is randomized. Subjects must not be randomized into the trial if a blood sample cannot be obtained. Serum should be collected, processed, and shipped according to the instructions provided in the laboratory manual. All serum specimens will be sent to PPD Vaccines and Biologics, LLC, Richmond, VA, USA, on dry ice.

7.1.3.1.2 Detection of IgG Antibody to VZV (gpELISA)

The purpose of the gpELISA is to detect IgG antibody to VZV before and after vaccination with VZV-containing vaccine(s). This is the primary assay used to evaluate the serological response to VZV-containing vaccine(s). This method detects antibodies to VZV glycoprotein (gp), which has been purified from 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 [13] [14] [15]. Serum sample titers as determined by gpELISA are shown to correlate with neutralizing antibody titers [16].

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 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 was used to generate a standard curve.

7.1.3.2 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover main trial serum from immunogenicity testing stored for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue vaccination prior to completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

A subject's consent for Future Biomedical Research may be withdrawn by the subject's legally acceptable representative. A subject's consent may be withdrawn at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject'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 subject 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 trial data and results. No new analyses would be generated after the request is received.

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

7.1.4.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required trial visit and/or if the site is unable to contact the parent/legally acceptable representative, the following procedures are to be performed:

- The site must attempt to contact the parent/legally acceptable representative and reschedule the missed visit. If the parent/legally acceptable representative is contacted, the parent/legally acceptable representative 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 parent/legally acceptable representative at each missed visit (e.g., phone calls and/or a certified letter to the last known mailing address of the parent/legally acceptable representative or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

When the investigator or delegate needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the investigator or delegate must enter the intensity of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

Treatment/Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

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

delegate and the respective subject's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- 2°C to 8°C refrigerator with temperature-monitoring device
- –20°C freezer with temperature-monitoring device
- Centrifuge

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Screening procedures will be performed at Visit 1. A separate screening visit is not required.

7.1.5.2 Vaccination Visits

See Section 6.0 for details.

7.1.5.3 Post-trial (Visit 4: Follow-up Visit, and Visit 5: Follow-up Phone Call)

Visit 4 Follow-up Visit: Subjects will be required to return to the clinic 6 to 8 weeks after Vaccination 2.

Visit 5 Follow-up Phone Call: In addition, 6 months after Vaccination 2, a follow-up phone call will be made to determine if any serious adverse events or medically attended adverse events have occurred since Visit 4.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example),

symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of allocation/randomization through 14 days (42 days for live attenuated vaccines) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days (42 days for live attenuated vaccines) thereafter, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.2.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than 1 dose of trial vaccine administered within 24 hours.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious 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 adverse event using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator 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).

7.2.2 Immediate Reporting of Adverse Events to the Sponsor

7.2.2.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 2 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, 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 6 months (~180 days) following the second vaccination, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, 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).

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

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

or

2. A serious adverse event that is considered by an investigator who is a qualified physician to be vaccine related.

All subjects with serious adverse events must be followed up for outcome.

7.2.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, 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 14 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 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).

Events of clinical interest for this trial include:

- No ECIs are being collected for this trial.

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 2. The investigator's assessment of causality is required for each adverse event. Refer to Table 2 for instructions in evaluating adverse events.

Table 2 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination through Day 5 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose that:	
	†**Results in death; or**	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements; **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This 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 vaccine and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? 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 trial is a single-dose vaccine trial.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**	
Yes, there is a reasonable possibility of vaccine relationship.	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.	
No, there is not a reasonable possibility of vaccine relationship	Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, but before any final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before final database lock, will be documented in a supplemental statistical analysis plan and referenced in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.11.

Study Design Overview	A Phase 3, Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX™ Passage Extension 34 (PE34) Process Administered Concomitantly with M-M-R™ II
Treatment Assignment	This is a double-blind trial with 2 vaccination groups. Subjects will be randomized to VARIVAX™ PE34 process group and VARIVAX™ (2016 commercial product) group with the ratio 1:1.
Analysis Populations	Immunogenicity: Per-protocol (PP) and Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. The response rate, the proportion of subjects with VZV antibody titer ≥5 gpELISA units/mL 6 weeks Postvaccination 1 among subjects who were seronegative to VZV (titer <1.25 gpELISA units/mL) at baseline. 2. The GMT of VZV antibodies in subjects at 6 weeks Postvaccination 1.
Key Secondary Endpoints	The seroconversion rate, the proportion of subjects with VZV antibody titer ≥1.25 gpELISA units/mL 6 weeks Postvaccination 1 among subjects who were seronegative to VZV (titer <1.25 gpELISA units/mL) at baseline.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	For the primary hypothesis 1, VARIVAX™ PE34 process will be considered noninferior to VARIVAX™ (2016 commercial product) if the lower bound of the 2-sided 95% CI of difference in response rates (VARIVAX™ PE34 process minus VARIVAX™ [2016 commercial product]) excludes a decrease of 10 percentage points or more. This analysis will be assessed using the Miettinen and Nurminen method [17]. For the primary hypothesis 2, VARIVAX™ PE34 process will be considered noninferior to VARIVAX™ (2016 commercial product) if the lower bound of the 2-sided 95% CI of the GMT ratio (VARIVAX™ PE34 process/VARIVAX™ [2016 commercial product]) is >0.67. This

	analysis will be assessed using 2-sample t test based on the log-transformed Postvaccination 1 antibody titers. For the primary hypothesis 3, VARIVAX™ PE34 process will be considered acceptable if the lower bound of the 95% CI for the response rate is above 76.0%. This analysis will be assessed using the exact CI method for a single binomial proportion given in Collett [18].
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints include the rate of fever (temperature ≥102.2°F [≥39.0°C] oral equivalent) from Days 1 to 42 after each vaccination; varicella-, zoster-, measles-, or rubella-like rashes or mumps-like symptoms, and injection-site rashes occurring within Days 1 to 42 after each vaccination; and solicited injection-site reactions (redness, swelling, pain/tenderness) within Days 1 to 5 after each vaccination. For Tier 1 events, inferential testing for statistical significance with *p* values and 95% CIs will be provided for between-group comparisons. Any adverse experiences (specific terms as well as system organ class [SOC] terms) that are not pre-specified as endpoints of particular interest will be classified as belonging to Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by vaccination group are provided for Tier 3 safety parameters. Analyses will be performed using the Miettinen and Nurminen method [17].
Interim Analyses	No interim analyses are planned for this trial.
Multiplicity	No multiplicity adjustment is planned as success of the trial requires success on both the noninferiority and acceptability hypotheses.
Sample Size and Power	The planned sample size is ~600 subjects in total (~300 in each group). Assuming 80% evaluability, 90% Postvaccination 1 response rates, and a standard deviation of 1.2 for the log-transformed Postvaccination 1 antibody titers, this trial has 94.1% power for demonstrating noninferiority of the response rate, 95.8% power for demonstrating noninferiority of the GMT, and >99.9% power for demonstrating acceptability of the response rate at an overall 2-sided 5% α-level. The overall power for the primary immunogenicity hypotheses is estimated to be 90% (= 0.941 × 0.958 × >0.999).

8.2 Responsibility for Analyses/In-house Blinding

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

This trial will be conducted as a double-blind trial under in-house blinding procedures. The official final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for trial treatment assignment.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the trial are stated in Section 3.0.

8.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated for between-group differences are described below.

8.4.1 Immunogenicity Endpoints

The primary endpoints for VZV immunogenicity will be the antibody response rates and GMTs after the first dose of VARIVAX™ in subjects who were initially seronegative to VZV at baseline.

The response rate and GMT endpoints and the criteria for baseline seronegativity are defined below:

- The response rate is the percentage of subjects with VZV antibody titer ≥5 gpELISA units/mL 6 weeks Postvaccination 1 among subjects who were seronegative to VZV (titer <1.25 gpELISA units/mL) at baseline.

- The postvaccination antibody GMTs 6 weeks Postvaccination 1.

In addition, the VZV seroconversion rate (defined as the proportion of subjects with baseline VZV titer <1.25 gpELISA units/mL and with postvaccination VZV titer ≥1.25 gpELISA units/mL) will be summarized after the first dose. For subjects who are initially seropositive (baseline VZV antibody titer ≥1.25 gpELISA units/mL), the geometric mean fold rise (GMFR) and the percentage of subjects achieving ≥4-fold rise in antibody titer from baseline will be summarized after the first dose.

8.4.2 Safety Endpoints

Refer to Section 4.2.3.2 for the description of the safety measures in this trial.

The key safety endpoints evaluated as Tier 1 events are as follows: the rate of elevated temperature from Days 1 to 42 after each vaccination; varicella-, zoster-, measles-, or rubella-like rashes or mumps-like symptoms, and all injection-site rashes occurring within Days 1 to 42 after each vaccination, and all solicited injection-site reactions (redness, swelling, pain/tenderness) occurring within Days 1 to 5 after each vaccination.

8.5 Analysis Populations

8.5.1 Immunogenicity Analysis Populations

8.5.1.1 Per-protocol Population

The primary immunogenicity analyses will be based on the PP population. The PP population consists of those subjects who are not considered as protocol violators. Violations include but are not limited to: failure to receive the full, scheduled doses (at least

90 days between doses 1 and 2) of correct clinical material and lack of valid serology results available from 27 to 84 days following the first dose. The day range for inclusion of postvaccination blood samples in the statistical analysis is wider than the visit window provided earlier in this protocol (+ 14 days for the 6-week serology testing), but is being used to be consistent with other studies evaluating VZV-containing vaccines.

In addition to meeting the PP population requirements, the primary analysis requires specific baseline criteria be met for VZV: baseline VZV antibody titer <1.25 gpELISA units/mL. Additional immunogenicity summaries will be made for subjects who meet the PP population requirements but do not meet the baseline antibody requirement for VZV (e.g., a summary of Postvaccination 1 VZV immunogenicity in otherwise PP subjects who have a baseline VZV antibody titer ≥1.25 gpELISA units/mL; see Section 8.6.1.4 for details).

Supportive summaries at Postvaccination 1 will also be made for the PP population, as described in Section 8.6.1.4.

The final determination on protocol violations, and thereby the composition of the PP population, will be made before unblinding of the database and will be documented in a separate memo.

8.5.1.2 Full Analysis Set

A supportive summary and analysis for VZV immunogenicity will be based on the FAS. The FAS population consists of all randomized subjects with a valid serology measurement, regardless of protocol violations. Subjects will be included in the vaccination group to which they are randomized for the FAS population. As a supportive analysis, the primary immunogenicity hypotheses will be evaluated on the FAS population in subjects meeting the VZV baseline antibody requirement to assess the robustness of the primary conclusions based on the PP population.

8.5.2 Safety Analysis Population

The ASaT population will be used for the analysis of safety data in this trial. The ASaT population consists of all randomized/allocated subjects who received at least 1 dose of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received (e.g., a subject who was randomized to Group 1 but received all vaccines according to the Group 2 schedule will be summarized with Group 2 subjects). Subjects who receive a mixed regimen (e.g., received VARIVAX™ PE34 process at Visit 1, but received VARIVAX™ [2016 commercial product] at Visit 3) will have their Postvaccination 1 safety data summarized with the group corresponding to the vaccine(s) received (for this example, with Group 1 subjects), and subsequent safety data summarized separately from the Postvaccination 2 summary for Group 1 and Group 2 subjects.

8.6 Statistical Methods

To control the overall type I error rate at $\alpha = 0.025$ (1-sided) and since success of the trial requires success on 3 hypotheses (2 noninferiority and 1 acceptability), each individual hypothesis test will be evaluated at $\alpha = 0.025$ (1-sided).

For the safety analyses, unless otherwise specified, all statistical tests will be conducted at $\alpha = 0.05$ level (2-sided).

8.6.1 Statistical Methods for Immunogenicity Analysis

8.6.1.1 Noninferiority of Postvaccination 1 VZV Antibody Response (Primary Hypothesis 1)

For the primary hypothesis concerning the noninferiority of the Postvaccination 1 antibody response rate for recipients of VARIVAX™ PE34 process compared with VARIVAX™ (2016 commercial product), a 1-sided test for noninferiority in 2 binomial proportions will be performed at the $\alpha = 0.025$ (1-sided) level.

The statistical hypothesis that will be evaluated is:

H_0: $p_1 - p_2 \leq -\delta$ versus H_1: $p_1 - p_2 > -\delta$,

where H_0 is the null hypothesis, H_1 is the alternative hypothesis, p_1 and p_2 are the true antibody response rates for the subjects in VARIVAX™ PE34 process and control groups, respectively, and δ is the pre-specified difference between the 2 proportions. The pre-specified difference between the 2 proportions (δ) is 0.10 (10 percentage points).

This analysis will be unstratified and the test statistic, *p* value, and corresponding 95% CIs will be calculated using the Miettinen and Nurminen method, an unconditional, asymptotic method [17]. The response rate in subjects receiving a single dose of VARIVAX™ PE34 process will be considered noninferior to the control group if the 1-sided *p* value for the associated noninferiority test is <0.025. This criterion is equivalent to requiring the lower bound of the 2-sided 95% CI for the difference in rates (Group 1 minus Group 2) exclude a decrease of 10 percentage points or more.

This analysis will be conducted on the PP population and the FAS population; however, the PP population is the primary population for the assessment of the hypotheses.

8.6.1.2 Noninferiority of Postvaccination 1 VZV Antibody GMT (Primary Hypothesis 2)

For the secondary hypothesis concerning the noninferiority of the Postvaccination 1 VZV antibody, GMT for recipients of VARIVAX™ PE34 process compared with VARIVAX™ (2016 commercial product), a 1-sided test for noninferiority in the VZV antibody GMT will be performed at the $\alpha = 0.025$ level (1-sided).

The statistical hypothesis for the noninferiority of the antibody GMT is:

H_0: $GMT_1/GMT_2 \leq 0.67$ versus H_1: $GMT_1/GMT_2 > 0.67$,

where GMT_1 is the GMT for recipients in Group 1 receiving VARIVAX™ PE34 process and GMT_2 is the GMT for recipients in Group 2 receiving VARIVAX™ (2016 commercial product). A ratio of 0.67 corresponds to a 1.5-fold decrease in GMT in Group 1 compared with Group 2. Rejecting the null hypothesis (H_0) at the 1-sided $\alpha = 0.025$ level corresponds to the lower bound of the 2-sided 95% CI for the GMT ratio (Group 1/Group 2) being >0.67.

The GMT ratio (VARIVAX™ PE34 process/VARIVAX™ [2016 commercial product]) along with a 2-sided 95% CI and *p* value will be determined at week 6 Postvaccination 1. Assuming normality of the log antibody titers, a 2-sided 95% CI for the difference in the means of the log titers (VARIVAX™ PE34 process minus VARIVAX™ [2016 commercial product]) will be constructed based on the t-distribution. The CI of the GMT ratio (VARIVAX™ PE34 process/VARIVAX™ [2016 commercial product]) will then be provided by exponentiating the endpoints of the CI for the difference in log titers.

This analysis will be conducted on the PP and FAS populations; however, the PP population is the primary population for the assessment of the hypotheses.

8.6.1.3 Acceptability of Immune Response (Primary Hypothesis 3)

The primary hypotheses also involve whether or not subjects in Group 1 of VARIVAX™ PE34 process demonstrate an acceptable antibody response Postvaccination 1 to VZV (Hypothesis 3). An acceptable antibody response to VZV is defined as a response rate that is at least 76.0%. A hypothesis of H_0: $p \leq p_0$ will be tested against the alternative H_1: $p > p_0$, where p is the antibody response rate after a single dose and p_0 is the hypothesized rate to be ruled out (76.0% for VZV). A 1-sided, 1-sample exact binomial test will be conducted at $\alpha = 0.025$ significance level. Rejection of the null hypothesis will lead to a conclusion of an acceptable antibody response to VZV. This is equivalent to the lower bound of the 1-sample 2-sided 95% CI being >76.0%. The 1-sample 2-sided CIs will be computed using the exact CI method for a single binomial proportion given in Collett [18].

This analysis will be conducted on the PP population and the FAS population; however, the PP population is the primary population for the assessment of the hypotheses.

The strategy to address multiplicity issues with regard to multiple primary immunogenicity endpoints and primary immunogenicity hypotheses is described in Section 8.8 – Multiplicity.

8.6.1.4 Secondary Summaries

In addition to the analysis described in Sections 8.6.1.1, 8.6.1.2, and 8.6.1.3 supporting the primary hypotheses, the following supportive summaries and figures will be presented for all subjects in the PP and FAS populations (where noted) with Postvaccination 1 immunogenicity data collected:

- The observed VZV antibody response rates (the percent of subjects with VZV titer ≥5 gpELISA units/mL) will be summarized by vaccination group at Postvaccination 1, along with 2-sided 95% CIs. The CIs will be computed using the exact CI method for a single binomial proportion given in Collett [18]. This will be computed on the PP population of subjects (with baseline antibody titer restriction) and the FAS population (with baseline antibody titer restriction).

- The observed VZV seroconversion rate (the percent of subjects with VZV titer ≥1.25 gpELISA units/mL) will be summarized by vaccination group at Postvaccination 1, along with 2-sided 95% CIs. The CIs will be computed using the exact method for a single binomial proportion given in Collett [18]. This will be computed on the PP population of subjects (with baseline antibody titer restriction) and the FAS population (with baseline antibody titer restriction).

- The observed VZV GMTs will be summarized by vaccination group at Postvaccination 1, along with 2-sided 95% CIs. The GMTs will be calculated by taking the natural log-transformation of the antibody titer, computing the arithmetic mean, and back-transforming. The CIs for the GMTs will be based on the natural log-transformed titers and the t-distribution. This will be computed on the PP population of subjects (with baseline antibody titer restrictions) and on the FAS population (with baseline antibody titer restrictions).

- For subjects who are seropositive at baseline (≥1.25 gpELISA units/mL for VZV), the following parameters and 95% CIs will be summarized at Postvaccination 1 by vaccination group: the GMT, the antibody response rate, the GMFR from baseline, and the percent of subjects with ≥4-fold rise in antibody titer from baseline. Similar methodology, as described previously, will be used for this summary. This will be computed on the PP and FAS populations (in subjects with baseline VZV antibody titer ≥1.25 gpELISA units/mL). The CIs will only be calculated if there are at least 5 subjects who are seropositive to a respective antigen.

- For subjects in the PP population only, graphical displays of the reverse cumulative distribution function of antibody titers will be illustrated by vaccination group.

The key immunogenicity analyses are summarized in Table 3.

Table 3 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary (Hypothesis 1 & 2):				
Noninferiority of the Postvaccination 1 VZV antibody response rates in Group 1 compared with Group 2	P (PP) S (FAS)	Miettinen and Nurminen‡ approach; tested at $\alpha = 0.025$ (1-sided); corresponding 95% CIs for risk difference	PP FAS	Observed data only
Noninferiority of the Postvaccination 1 VZV antibody GMTs in Group 1 compared with Group 2	P (PP) S (FAS)	2-sample mean difference and 95% CI and *p* values based on log-transformed titers and t-distribution	PP FAS	Observed data only
Primary (Hypothesis 3):				
Acceptability of the Postvaccination 1 VZV antibody response rate in Group 1	P (PP) S (FAS)	Exact 1-sample binomial; tested at $\alpha = 0.025$ (1-sided); corresponding 95% CIs	PP FAS	Observed data only
Secondary:				
Summary of Postvaccination 1, VZV antibody response rates and VZV seroconversion rates for both groups	P (PP) S (FAS)	Exact 1-sample binomial methodology, 95% CIs	PP FAS	Observed data only
Summary of Postvaccination 1 VZV antibody GMTs	P (PP) S (FAS)	1-sample mean and 95% CI based on log-transformed titers and t-distribution	PP FAS	Observed data only
Summary of Postvaccination 1 VZV antibody response rates, GMTs, GMFR from baseline and % ≥ 4-fold rise from baseline in subjects initially seropositive for both groups	P (PP) S (FAS)	For rates, 1-sample binomial methodology, 95% CI For continuous variables, one-sample mean and 95% CI based on t-distribution	PP FAS	Observed data only

†P = primary approach; S = supportive approach.

‡Miettinen and Nurminen method [17].

8.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all safety data collected throughout the trial.

The analysis of safety results will follow a tiered approach (Table 4). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of particular interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with *p* values and 95% CIs provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by vaccination group are provided for Tier 3 safety parameters.

Any adverse experiences (specific terms as well as system organ class [SOC] terms) that are not pre-specified as endpoints of particular interest will be classified as belonging to Tier 2 or Tier 3, based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any vaccination group exhibit the event; all other adverse experiences will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and, thus, would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

For this protocol, the following are considered Tier 1 events: elevated temperatures (maximum reported temperature ≥102.2°F [≥39.0°C] oral equivalent) within Days 1 to 42 after each vaccination; vaccine-specific measles-, rubella-, varicella-, zoster-like rashes, mumps-like symptoms, and injection-site rashes occurring within Days 1 to 42 after each vaccination; and solicited injection-site reactions (redness, swelling, pain/tenderness) within Days 1 to 5 after each vaccination. In addition, the broad clinical categories consisting of the percentage of subjects with any adverse experience, a vaccine-related adverse experience, a serious adverse experience, an adverse experience that is both vaccine-related and serious, and who discontinued due to an adverse experience will be considered Tier 2 endpoints. The *p* values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) will be provided for between-group differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method [17].

Extended Safety Follow-up Period (Day 133 [+14 days] to Day 271 [+14 days])

For the extended safety follow-up period, a summary will be provided of the number of subjects in each vaccination group who report a serious adverse experience or a medically attended adverse experience. For this extended safety follow-up period, these events will be treated as Tier 2 events, with 95% CIs being presented for the between-group risk differences in the percentage of subjects reporting these events. For serious adverse experiences, a

summary along with a between-group comparison will also be provided for the entire trial (i.e., from enrollment through 180 days Postvaccination 2).

Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[†]	*p* Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Rate of elevated temperatures (≥ 102.2°F [39.0°C]) [‡] from Days 1 to 42 postvaccination	X	X	X
	Vaccine-specific systemic rashes (measles-like, rubella-like, varicella-like, zoster-like), mumps-like symptoms, and injection-site rashes Days 1 to 42 postvaccination	X	X	X
	Injection-site reactions (redness, swelling, and pain/tenderness) Days 1 to 5 postvaccination	X	X	X
Tier 2	Any AE Days 1 to 42 postvaccination		X	X
	Any serious AE Days 1 to 42 postvaccination		X	X
	Any vaccine-related[§] AE Days 1 to 42 postvaccination		X	X
	Any serious and vaccine-related[§] AE Days 1 to 42 postvaccination		X	X
	Discontinuation due to AE Days 1 to 42 postvaccination		X	X
	Specific systemic AEs[¶] and SOCs (incidence ≥ 4 subjects in one of the vaccination groups) during Days 1 to 42 postvaccination and injection-site reactions[¶] (incidence ≥ 4 subjects in one of the vaccination groups) Days 1 to 5 postvaccination and Days 1 to 42 postvaccination		X	X

Safety Tier	Safety Endpoint[†]	*p* Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 3	Specific systemic AEs[¶] and SOCs (incidence <4 subjects in all of the vaccination groups) during Days 1 to 42 postvaccination and injection-site reactions[¶] (incidence <4 subjects in all of the vaccination groups) Days 1 to 5 and Days 1 to 42 postvaccination			X
	Maximum temperature summary (Brighton Collaboration Cutpoints) by day range: Days 1 to 42, Days 1 to 5, Days 6 to 13, Days 14 to 28, and Days 29 to 42 postvaccination			X
	Distribution of maximum size (for injection-site redness and swelling Days 1 to 5 postvaccination) and distribution of maximum intensity (for all other injection-site reactions Days 1 to 5 postvaccination and all systemic AEs Days 1 to 42 postvaccination)			X

[†] Adverse experience references refer to Clinical AEs.
[‡] For reporting purposes, temperatures will be converted to oral equivalent by adding 1.0°F to axillary temperatures and subtracting 1.0°F from rectal temperatures.
[§] Determined by the investigator to be related to the vaccine.
[¶] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
X = results will be provided.

The between-group comparisons described above will be made between Group 1 and Group 2 for each postvaccination follow-up period. This will be done by performing separate comparisons between VARIVAX™ PE34 process and VARIVAX™ (2016 commercial product) vaccination groups for the 42 days after receipt of the first vaccination and for the 42 days after receipt of the second vaccination. For serious adverse experiences, a summary along with a between-group comparison will also be provided for the entire primary trial phase (i.e., the combined 42-day periods after both vaccinations).

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Subject characteristics of age, gender, and race/ethnicity will be summarized by vaccination group for all subjects who entered the trial. In addition, baseline serostatus for VZV will be presented by vaccination group.

The number (%) of subjects with specific prior medications in any vaccination group within 14 days before the first vaccination will be summarized by vaccination group. Also, the number (%) of subjects with specific prior vaccinations (incidence rate >0% in any vaccination group) within 14 days before each vaccination will be summarized.

The number (%) of subjects with specific concomitant medications (incidence rate ≥5% in any vaccination group) within 42 days after each visit will be summarized by vaccination group. Also, the number (%) of subjects with specific concomitant vaccinations (incidence rate >0% in any vaccination group) within 42 days after each visit will be summarized by vaccination group.

No statistical comparisons will be made between vaccination groups. Instead, balance between vaccination groups with respect to subject characteristics will be determined by observation.

A detailed subject accounting will be provided at each vaccination visit and for each follow-up period. This accounting will describe the number of subjects randomized at trial start, the number vaccinated at each vaccination visit, and the number of discontinuations and withdrawals during each safety follow-up period. This subject accounting will also indicate the number of subjects who completed the trial.

No other analyses are planned for this trial.

8.7 Interim Analyses

No interim analyses are planned for this trial.

8.8 Multiplicity

Because success of the trial requires success on both the noninferiority and acceptability hypotheses, no adjustment for multiplicity is required across the hypothesis tests.

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Immunogenicity Analyses

This trial will randomize ~300 subjects into Group 1 (VARIVAX™ PE34 process) and ~300 subjects into Group 2 (VARIVAX™ [2016 commercial product]), and this trial has 94.1% power for demonstrating noninferiority of the VZV response rate, 95.8% power for demonstrating noninferiority for antibody GMTs, and >99.9% power for demonstrating acceptability of the VZV response rate at an overall 1-sided 2.5% α -level.

The sample size and power calculations are based on the following assumptions:

- 10% of subjects will be nonevaluable after the first vaccination (due to lost to follow-up or other reasons, excluding baseline VZV serostatus),
- For the VZV analysis, 10% will have baseline VZV antibody titers >1.25 gpELISA units/mL, resulting in an expected overall nonevaluability rate for the VZV Postvaccination 1 primary analyses of 20% (= 10% + 10%), and
- The expected VZV Postvaccination 1 response rate in both groups is assumed to be 90% based on prior experience with VARIVAX™ in this age group.
- The assumed standard deviation of the log-transformed VZV antibody titer is 1.2 based on previous studies of VARIVAX™.

If the assumptions listed above are observed at the final analysis, the lower bounds for the 95% CIs for addressing the 3 primary hypotheses listed in Section 8.6.1 would be −5.4% for the noninferiority of response rates comparison (Hypothesis 1), 0.81 for the noninferiority of GMTs comparison (Hypothesis 2), and 86.2% for the acceptability of the response rate (Hypothesis 3).

Because success of the trial requires that the statistical criteria be met for both the noninferiority and acceptability hypotheses, the overall power for the primary immunogenicity hypotheses is estimated to be 90% (= 0.941 × >0.999 × 0.958).

8.9.2 Sample Size and Power for Safety Analyses

For safety comparisons Postvaccination 1, all subjects are expected to be evaluable. If no serious adverse event is observed among the 300 subjects in each vaccination group, this trial provides 97.5% confidence that the true serious adverse event rate is <1.22% (1 out of every 81 subjects).

The probability of observing at least 1 serious adverse event in this trial depends on the number of subjects enrolled and the incidence rate of serious adverse events in the general population. If the incidence rate of a serious adverse event is 1 of every 186 recipients of the vaccine (0.54%), then there is an 80% chance of observing at least 1 such serious adverse event among 300 subjects in the vaccine group. If the incidence rate is 1 of every 433 recipients (0.23%), there is a 50% chance of observing at least 1 serious adverse event.

For safety comparisons, risk differences between any 2 vaccination groups that could be detected with an 80% probability are summarized in Table 5 for a variety of hypothetical true incidence rates. These calculations assume there are 300 subjects for safety in both groups and are based on a 2-sided significance level of $\alpha = 0.05$. No multiplicity adjustments were made in these calculations.

Table 5 Differences in Incidence of Adverse Event Rates between the Two Vaccination Groups That Can be Detected With an ~80% Probability and a Two-Sided Significance Level of 0.05 Postvaccination 1

True Incidence Rate of Adverse Events in the Control Group (Group 2)	True Incidence Rate of Adverse Events in the Investigational Group (Group 1)	Detectable Percentage Point Difference in Incidence Rates of Adverse Events
N = 300	N = 300	
1%	4.8%	3.8
2%	6.6%	4.6
5%	11.2%	6.2
10%	17.9%	7.9
15%	24.0%	9.0
20%	29.9%	9.9
30%	40.9%	10.9

For safety comparisons Postvaccination 2, it is expected that ~5% of subjects will fail to return for the second vaccination phase, which results in 285 subjects in each group. If no serious adverse event is observed among the 285 subjects in each vaccination group, this trial provides 97.5% confidence that the true serious adverse event rate is <1.29% (1 out of every 77 subjects).

The probability of observing at least 1 serious adverse event in this trial depends on the number of subjects enrolled and the incidence rate of serious adverse events in the general population. If the incidence rate of a serious adverse event is 1 of every 177 recipients of the vaccine (0.56%), then there is an 80% chance of observing at least 1 such serious adverse event among 285 subjects in the vaccine group. If the incidence rate is 1 of every 411 recipients (0.24%), there is a 50% chance of observing at least 1 serious adverse event.

For safety comparisons, risk differences between any 2 vaccination groups that could be detected with an 80% probability are summarized in Table 6 for a variety of hypothetical true incidence rates. These calculations assume there are 285 subjects for safety in both groups and are based on a 2-sided significance level of $\alpha = 0.05$. No multiplicity adjustments were made in these calculations.

Table 6 Differences in Incidence of Adverse Event Rates Between the Two Vaccination Groups That Can be Detected With an ~80% Probability and a Two-Sided Significance Level of 0.05 Postvaccination 2

True Incidence Rate of Adverse Events in the Control Group (Group 2)	True Incidence Rate of Adverse Events in the Investigational Group (Group 1)	Detectable Percentage Point Difference in Incidence Rates of Adverse Events
N=285	N=285	
1%	5.0%	4.0
2%	6.8%	4.8
5%	11.4%	6.4
10%	18.1%	8.1
15%	24.3%	9.3
20%	30.2%	10.2
30%	41.2%	11.2

8.10 Subgroup Analyses

To determine whether the vaccination effect is consistent across various subgroups, the estimate of the between-group effect (with a nominal 95% CI) for the primary immunogenicity endpoints will be estimated and may be plotted within each category of the following classification variables:

- Sex (female, male)
- Race

The consistency of the vaccination effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

In addition, a summary of Tier 1 and Tier 2 adverse experiences will be provided for sex and race.

8.11 Extent of Exposure

The number of subjects vaccinated at each vaccination visit will be summarized by vaccination group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 7.

Table 7 Product Descriptions

Product Name	Dosage Form
Varicella Virus Vaccine Live[a] PE34 process[b]	Single 0.5 mL dose suspension for subcutaneous injection after reconstitution
Varicella Virus Vaccine Live[a,b] (2016 commercial product)	Single 0.5 mL dose suspension for subcutaneous injection after reconstitution
Measles, Mumps, and Rubella Virus Vaccine Live[b,c]	Single 0.5 mL dose suspension for subcutaneous injection after reconstitution
Sterile Diluent for Reconstitution of Merck Live Virus Vaccines (Sterile Water)	0.7 mL sterile solution for reconstitution

[a]Varicella Virus Vaccine Live = VARIVAX™.
[b]Potency conforms to product standards as stated in the respective product inserts.
[c]Measles, Mumps, and Rubella Virus Vaccine Live = M-M-R™ II.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Blinded, single-dose vials of VARIVAX™ PE34 process and VARIVAX™ (2016 commercial product) will be supplied to the clinical sites. Open-label, single-dose vials of M-M-R™ II and Sterile Diluent for reconstitution will be supplied to the clinical sites. No subject-specific kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask vaccine identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign vaccine to subjects 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 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 institutional review board, ethics review committee (IRB/ERC) 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 trial 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.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject 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 subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

10.2 Compliance with Financial Disclosure Requirements

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.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial 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 trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck 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

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

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 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 trial as outlined in Section 7.1.3.2 – Future Biomedical Research Samples 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. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial 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 subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (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 trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject 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 subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

At the clinical trial 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 subject identifiers and this unique code will be held at the trial 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 (e.g., 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 sub-trial. 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

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject'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 subject 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 trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject'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 trial 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 trial, the trial 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 trial 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 Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject 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 subjects. Subjects 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 subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.

The Sponsor has developed strict security, policies and procedures to address subject 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 e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. 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. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood Volumes Collected by Trial Visit and by Sample Types

Trial Visit	Visit 1	Visit 2	Visit 3	Visit 4
Blood for immunogenicity testing	3	3	—	—
Expected total (mL)	3	3	—	—

12.4 Scripted Questionnaire to Be Used by Site Personnel to Obtain Serious Adverse Experience and Medically Attended Adverse Event Information

The following script is to be used at the Phone Call at Day 271 (180 days after Dose 2) in order to probe for any serious adverse experiences and medically attended adverse events that were not previously reported by the subject's parent/legally acceptable representative from Visit 4 (Day 133) through Day 271.

It is the responsibility of the Investigator to carefully assess the information and make a determination whether the adverse experience meets one or more criteria for being reported as a serious adverse experience. Serious adverse experiences and medically attended adverse events identified through the interview process should be reported to the Sponsor/Sponsor Representative.

Questionnaire:

Since the last visit,

1. Has your child been admitted to a hospital?

2. Has your child experienced a life-threatening episode or an important medical event that required attendance in the Emergency Room or a health care provider's office?

3. Has your child seen your doctor, nurse, or health care provider for any other reason other than a well-child visit?

4. Did your child have any medical conditions before you agreed to participate in the trial that have become worse or have required more frequent visits to a health care provider since the last visit?

5. Has your child developed cancer?

6. Has your child developed a new medical condition that I am not aware of?

If the answer to any of the questions above is "yes", the interviewer will determine if the event is a serious adverse experience or a medically attended event and if so, will gather all related information and transcribe onto the appropriate eCRFs.

For each serious adverse experience that is identified through the interview process, information from all available sources, including subject/legally acceptable representative report, subject medical records, hospital discharge summary, and death certificate should be sought to provide a complete description of the adverse experience. All pertinent information must be recorded in the database and retained in the subject's file including, but not limited to:

- Serious adverse experience term
- Onset date
- Causality
- Outcome

- The seriousness criteria that the adverse experience met:
  - death
  - caused hospitalization or prolonged existing hospitalization
  - persistent or significant disability
  - life-threatening adverse experience
  - cancer
  - due to an overdose
  - congenital anomaly
  - other medical adverse experience
- Hospitalization admission date
- Hospital discharge date
- Concomitant medications/vaccinations or changes in concomitant medications associated with the serious adverse experience
- Concurrent conditions
- Other medical history
- Procedures associated with the serious adverse experience
- Laboratory results

12.5 List of Abbreviations and Definitions of Terms

Term	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event or adverse experience *(used interchangeably)*
ASaT	All Subjects As Treated
CI	confidence interval
CID	component identification number
CSR	clinical study report
DOD	delta optical density
DTaP	Diphtheria, Tetanus, and Acellular Pertussis
DNA	deoxyribonucleic acid
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
FSA	full analysis set
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
gp	glycoprotein
gpELISA	glycoprotein enzyme-linked immunosorbent assay
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HZ	herpes zoster
IgG	immunoglobulin G
IPV	inactivated poliovirus
IRB	institutional review board
IVRS	interactive voice response system
IWRS	integrated web response system
M M-R™ II	measles, mumps, and rubella virus vaccine live, Merck

Term	Definition
OD	optical density
PP	Per-protocol Population
PRO	patient-reported outcome
ProQuad™	measles, mumps, rubella, and varicella virus vaccine live, Merck
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TCC	tissue culture control
VARIVAX™	varicella virus vaccine live (Oka/Merck); A210
eVRC	electronic vaccination report card
VZV	varicella zoster virus
WHO	World Health Organization
ZOSTAVAX™	zoster vaccine live, Merck

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	