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One Merck Drive

P.O. Box 100

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TITLE:

A Phase III Randomized, Placebo-Controlled, Clinical Trial to Study the Safety and Efficacy of V212 in Adult Patients with Solid Tumor or Hematologic Malignancy

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: III

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INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

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SUMMARY OF CHANGES**PRIMARY REASON FOR THIS AMENDMENT:**

Section Numbers	Section Titles	Description of Changes	Rationale
1.2	Indication	Removed hematologic malignancy (HM) population.	All changes in this table were made based upon the projected case accrual rate in the STM arm and/or the outcome of the first interim analysis which demonstrated clear evidence of futility in the HM population. An interim analysis for futility was conducted for both the HM and STM populations on 29-Oct-2014. This analysis demonstrated clear evidence of futility in the HM arm. On 04-Nov-2014, enrollment and vaccination in the HM arm was stopped. Close-out procedures began in the HM population on 19-Nov-2014.
1.3	Summary of Rationale	Clarification that there will be no further interim analysis for the solid tumor malignancy (STM) population.	
1.4	Summary of Study Design	Added description of outcome of interim analysis for futility. Updated the target herpes zoster (HZ) case accrual to 90 from 210 for the STM population and removed the second interim analysis. Clarified study duration time frame.	
1.7	Study Flow Chart	Removed gpELISA blood sample text related to STM enrichment following first interim analysis in footnote marked with ^{††} .	
2.1.2	Primary Hypotheses	As only one primary hypothesis will be tested for the STM population, testing alpha level was changed to 0.0125 (from 0.0115).	
2.1.3	Secondary Objectives	Removed testing lower bound of VE=10% for a single population.	
2.1.3	Secondary Objectives	Edited to test secondary objectives for HM and STM	

		separately.	
2.1.4	Exploratory Objectives	All objectives in HM population were changed to exploratory and, when applicable, exploratory objectives will be tested separately in the HM and STM populations.	
2.4.1	Summary of Study Design	Modified text to reflect outcome of interim analysis for futility. Edited to reflect that study is continuing with STM population only and second interim analysis will not be performed.	
2.5.3	Immunogenicity Measurements	Removed mention of sample size enrichment.	
2.7.1	Efficacy	Updated the hypothesis and endpoints and statistical analysis method for primary/secondary efficacy analyses. With only one study population and no enrichment, there are no statistical concerns regarding type I error rate inflation and biased VE estimate. To be aligned with V212-001, Cox proportional hazards regression model will be used.	
2.7.4	Power and Sample Size	Updated target case accrual for STM population and power statement and revised the feasibility assessment language.	
2.7.5	Interim Analysis	Placed text describing plan for interim analysis which already occurred in Appendix 6.3. Removed the	

		second interim analysis and population enrichment.	
3.1.2	Rationale for this Study	Added text describing outcome of interim analysis.	
3.5.1	Responsibility for Analyses	Removed second interim efficacy analysis.	
3.5.3.1	Efficacy	Updated secondary endpoints and edited to test secondary/exploratory objectives for HM and STM separately for each population.	
3.5.5.1	Analysis of Vaccine Efficacy	Updated Table 3.2.	
3.5.5.1.1	Analysis of Vaccine Efficacy on Incidence of HZ Cases	Updated the hypothesis and endpoints and statistical analysis method for primary analysis. Added statement that Efron's method will be used to handle ties in event times.	
3.5.5.1.2	Analysis of Vaccine Efficacy on Secondary Efficacy Endpoints	Updated the endpoints and statistical analysis method.	
3.5.5.1.3	Analysis of Vaccine Efficacy on Exploratory Endpoints	Edited to test exploratory endpoints separately for each population.	
3.5.5.1.4	Analysis on the Durability of Vaccine Efficacy	Edited to evaluate durability separately for each population.	
3.5.5.2	Analysis of Vaccine Immunogenicity	Removed the mention of population enrichment.	
3.5.6	Multiplicity	Updated the testing alpha	

		level and removed multiplicity adjustment for interim efficacy.	
3.5.7.1	Efficacy Analysis	Updated target case accrual for STM population and power statement and revised the feasibility assessment language.	
3.5.8	Interim Analysis	Removed second interim efficacy analysis and mention of enrichment.	
3.5.8.1	Interim Analyses of Futility/ Efficacy for Potential Early Study Termination	Modified text to reflect outcome of interim analysis. Removed second interim efficacy analysis and mention of enrichment.	

ADDITIONAL CHANGES FOR THIS AMENDMENT:

Section Numbers	Section Titles	Description of Changes	Rationale
1.7	Study Flow Chart	Updated footnote marked by (§) to reflect that one arm of the study may enter close-out based on DMC recommendation.	Clarity.
3.1.2.4	Rationale for the Immunogenicity Endpoint Measures	Applicable text revised	Revised to reflect change in central laboratory.
3.3.2	PCR Assay for Lesion Samples	Applicable text revised	
3.3.3	PCR Assay for Whole Blood Samples	Applicable text revised	
3.3.4	VZV Antibody gpELISA	Applicable text revised	
3	Protocol Details	Tables renumbered sequentially throughout Section 3.	Due to the deletion and addition of tables based on changes detailed in Summary of Changes.
6.2	Adverse Experience Toxicity Grading Scale	Added Note to Table 6-6 'Systemic AE Toxicity Grading Scale' stating events determined to be life-threatening or resulting in death are also assigned a Toxicity Grade = 4.	Updated for consistency with Data Entry Guidelines.

1. SUMMARY

1.1 TITLE

A Phase III Randomized, Placebo-Controlled, Clinical Trial to Study the Safety and Efficacy of V212 in Adult Patients with Solid Tumor or Hematologic Malignancy

1.2 INDICATION

The proposed indication for V212/inactivated varicella-zoster virus (VZV) vaccine is the prevention of herpes zoster (HZ) and HZ-related complications in immunocompromised patients with solid tumor malignancy (STM).

1.3 SUMMARY OF RATIONALE

HZ, known also as shingles, is a manifestation of reactivation of VZV¹, which, as a primary infection, produces chickenpox (varicella). Following initial infection, the virus remains latent in the spinal dorsal root or cranial sensory ganglia until it reactivates and replicates, producing HZ. ZOSTAVAX™ is the only currently-licensed intervention that can reduce the risk of developing HZ, postherpetic neuralgia (PHN), and the acute and chronic pain associated with HZ. ZOSTAVAX™ was developed by Merck Research Laboratories (MRL) for the prevention of HZ and its complications, especially HZ-related pain. However ZOSTAVAX™, a live attenuated vaccine, is contraindicated in immunocompromised patients.

The incidence of HZ in immunocompetent older adults (i.e., ≥ 60 years of age) is 7 to 11 per 1000 person-years [1]. Immunocompromised individuals have a higher incidence of HZ, and are at increased risk for developing severe and life-threatening complications [2-12]. Based on a MRL-sponsored epidemiology study conducted at Kaiser Permanente Northern California (KPNC) for HM and STM populations, the incidence rate of HZ is approximately 19 per 1000 for STM and ranges from 23 to 56 per 1000 person-years for HM [13]. Prevention of HZ disease in immunocompromised individuals, including those with HM or those with STM receiving chemotherapy, represents an area of significant medical need, since these immunocompromised individuals cannot receive the live attenuated zoster vaccine.

¹ Abbreviations frequently used in this protocol: CAC: Clinical Adjudication Committee; DMC: Data Monitoring Committee; HCT: hematopoietic cell transplant; HM: hematologic malignancy; HZ: herpes zoster; IC: immunocompromise; PHN: post-herpetic neuralgia; SAE: serious adverse event; STM: solid tumor malignancy; VRC: Vaccination Report Card; VZV: varicella-zoster virus.

Two proof-of-concept (POC) studies in hematopoietic cell transplant (HCT) recipients using heat-inactivated Oka/Merck varicella vaccine demonstrated: 1) reduced morbidity (i.e., extent and severity of HZ) following a 3-dose vaccine regimen and, 2) a decreased incidence of disease due to VZV reactivation, following a 4-dose vaccine regimen [14, 15]. The heat-treated VZV vaccine appeared generally safe. Overall, these two studies demonstrated that inactivated VZV vaccine given to recipients of HCT had a significant impact on the development of HZ.

Subsequently, Protocol 002, a randomized, double-blind, multicenter, immunogenicity and safety Phase I clinical study of V212 inactivated by heat-treatment was conducted in 4 distinct immunocompromised populations: recipients of HCT (allogeneic and autologous), patients infected with human immunodeficiency virus (HIV) with CD4 counts <200 cells/mm³, patients with HM and patients with STM receiving chemotherapy. The study demonstrated promising immunogenicity following a 4-dose regimen in the autologous-HCT, STM and HM populations, less robust responses in the HIV population, and poor responses in the allogeneic-HCT study population. No safety signals were identified in any of the immunocompromised populations studied [16].

Inactivation of the vaccine via the heat-treatment targets a reduction of VZV infectious particles to <10 plaque-forming units (PFU) per dose. Inactivation by gamma irradiation further reduces residual infectivity to <0.1 PFU per dose. Protocol 004, a randomized, double-blind, multicenter Phase I study to evaluate the safety, tolerability, and immunogenicity of V212 inactivated by gamma-irradiation and V212 inactivated by heat-treatment in healthy adults 50 to 59 years old, demonstrated that V212 inactivated by gamma-irradiation elicited acceptable immunogenicity and had an acceptable safety profile when administered to healthy individuals [17].

Protocol 011 is a Phase III study to assess the efficacy, safety, and immunogenicity of V212 inactivated by gamma irradiation in a larger population of adults with HM or STM receiving chemotherapy. The study will be conducted using a 4-dose regimen administered ~30 days apart, consistent with the vaccine regimen used in the Phase I study, Protocol 002 (rationale for the 4-dose regimen is provided in Section 3.1.2.2). The study will expand upon the experience of the earlier studies, including the POC studies and P002, which suggested that inactivated VZV vaccine administered as a 4-dose regimen is well-tolerated and immunogenic, and could provide substantial reduction in HZ incidence in HM and STM patients [14-16].

V212-011 is an adaptively designed study which included a planned interim analysis for futility when 50% of the targeted cases of HZ had accrued in each population. At this interim analysis, conducted 29-Oct-2014, clear evidence of futility was demonstrated for the primary endpoint in the HM arm. Thus, the HM arm is being closed and with this amendment, there will be no further interim analysis in the STM arm and the final analysis will be conducted on cases accrued in the STM arm only.

1.4 SUMMARY OF STUDY DESIGN

Approximately 5264 patients (~2568 HM patients; ~2696 STM patients), 18 years of age or older will be equally randomized to receive a 4-dose regimen of either V212 or placebo. (**Note: In India only, enrollment is restricted to patients 18 to 65 years of age.**) Patient allocation will be double-blinded, with in-house blinding procedures. Enrollment for this study is expected to be completed in approximately 36 months. Study duration is anticipated to be approximately 5 years from the date the first patient is enrolled.

This is an event-driven study based upon the occurrence of confirmed HZ cases. HZ rates will be monitored on an ongoing basis using the blinded database. The primary efficacy analysis will be conducted after at least 90 confirmed HZ cases have been accrued in the STM population. Patients will remain in the study from the time of enrollment until accrual of the targeted number (~90) of confirmed HZ cases. This study uses an adaptive design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. The study will be conducted based on 2 key efficacy milestones as listed below:

- When at least 50% of the required confirmed HZ cases have accrued for each population, HM and STM, interim futility analysis will be conducted for each group (completed 29-Oct-2014).
- When 90 confirmed HZ cases have accrued in the STM population, the database will be unblinded and the final efficacy analysis will be conducted. Of note, if the observed HZ case accrual rate indicates that more than 5 years of patient follow-up will be necessary to accrue the targeted number of confirmed cases, then the SPONSOR will consider it beyond the adjustment cap and terminate the study after approximately 5 years of patient follow-up have occurred (from the date the first patient is enrolled).

During the interim analysis, a futility analysis was conducted to assess whether efficacy met a pre-specified level. The analysis was conducted separately for each patient population (HM and STM) when at least 50% of required HZ cases had accrued in the corresponding population (29-Oct-2014). Analysis results were evaluated by the DMC with the following outcome:

HM population: solid statistical evidence of futility for the primary endpoint. Thus, enrollment and vaccination was stopped on 04-Nov-2014 and study close-out procedures in this population began on 19-Nov-2014.

STM population: no significant safety concerns nor a reason to stop the study due to futility.

The DMC recommended that the study in the STM population should proceed. A final case count of 90 will be targeted in this population which will provide adequate power for the primary endpoint without the need for enrollment of additional subjects.

Based on this adaptive design, the study may end in the following situations:

- 1) When the required number of confirmed HZ cases has accrued; or
- 2) If the decision is made to end the study early following a recommendation made by the DMC based on safety concerns; or
- 3) The HZ event rates will be monitored on an ongoing basis using the blinded database. If the observed HZ case accrual rate indicates that more than 5 years of patient follow-up will be necessary to accrue the targeted number of confirmed cases, then the SPONSOR will declare the trial infeasible and terminate the study after approximately 5 years of patient follow-up have occurred.

In any of these events, the study will begin to enter the close-out phase and no additional suspected cases of HZ will be accrued.

Safety information will be collected for all patients for the entire duration of the study as described in Section 2.6. In the event the study ends sooner than 1 year after the last vaccine dose is administered, the study will continue to follow all patients for safety and efficacy for a minimum duration of 1 year following the last dose of study vaccine.

Exploratory immunogenicity measurements will be conducted on a subset of patients, as described in Section 2.5, to assess the immunogenicity of the vaccine and attempt to investigate correlation of immune responses to the vaccine with clinical efficacy.

1.5 SAMPLE

This study will enroll men and women with a life expectancy of at least 12 months, who are varicella-history (or VZV-antibody) positive or based on regional epidemiology have a high likelihood of latent VZV infection, are not likely to undergo hematopoietic cell transplant (HCT) and

- are 18 years of age or older and receiving chemotherapy for STM or HM.

OR

- are 50 years of age or older* and have HM, not in remission, regardless of whether or not they are receiving chemotherapy.

***Note: In India only, enrollment is restricted to patients 18 to 65 years of age.**

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

All patients enrolled in the study will be randomized 1:1 to receive either V212 or placebo given as a 4-dose regimen. Placebo will be the vaccine stabilizer for the VZV vaccine with no virus antigen.

Dose 1 of V212 or placebo regimen will be administered at the time of enrollment (Day 1). Doses 2 through 4 will be administered approximately 30 days following each previous dose, in those patients who are not receiving chemotherapy or in those who are on a daily chemotherapy regimen. In those patients receiving cyclic chemotherapy, Dose 1 of V212 or placebo regimen should be administered approximately 5 days before the onset of any chemotherapy dose in the cycle. Doses 2 through 4 are to be administered approximately 20 to 40 days following the previous dose of study vaccine or placebo, with the condition that V212 or placebo be administered approximately 5 days prior to the upcoming dose of chemotherapy. See Sections 1.7 and 1.8 for all permitted visit windows.

Each dose of V212 or placebo will be administered as a 0.5-mL subcutaneous injection preferably in the deltoid region of the arm, alternating arms for each study vaccine or placebo dose, if possible.

1.7 STUDY FLOW CHART

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Periodic Efficacy Contact [†]	Periodic Safety Contact (SAE) [‡]	Study Close-out Visit [§]
	Prior to Study Procedures	Dose 1	Dose 2	Dose 3	Dose 4	28 days Postdose 4	Monthly	Every 3 months	
Visit window permitted (day)	N/A	Day 1	20 to 40 days post-dose 1	20 to 40 days post-dose 2	20 to 40 days post-dose 3	28 to 60 days post-dose 4 [#]	-7/+14 days	+/-30 days	N/A
Obtain Informed Consent	X								
Provide and Review Patient Identification Card		X							
Perform Physical Exam, including weight		X							
Collect Medical History		X							
Review Inclusion/Exclusion criteria		X							
Review Deferment Criteria			X	X	X				
Perform Pregnancy Test [¶]		X	X	X	X				
Assign Study Vaccine or Placebo using IVRS [#]		X	X	X	X				
Collect blood for gpELISA testing on all patients in the STM study group ^{††}		X				X			
Collect blood for IFN γ ELISPOT testing in ELISPOT substudy patients only ^{††}		X				X			
Administer Vaccine/Placebo		X	X	X	X				

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Periodic Efficacy Contact [†]	Periodic Safety Contact (SAE) [‡]	Study Close-out Visit [§]
	Prior to Study Procedures	Dose 1	Dose 2	Dose 3	Dose 4	28 days Postdose 4	Monthly	Every 3 Months	
Visit window permitted (day)	N/A	Day 1	20 to 40 days post-dose 1	20 to 40 days post-dose 2	20 to 40 days post-dose 3	28 to 60 days post-dose 4	-7/+14 days	+/-30 days	N/A
Educate patients on signs and symptoms of HZ		X	X	X	X	X	X		
Assess for occurrence of unreported symptoms of suspected HZ		X	X	X	X	X	X		X
Provide VRC and review instructions with patient ^{§§}		X	X	X	X				
Collect and review completed VRC with patient and collect information on adverse experiences			X	X	X	X			
Ascertainment of Serious Adverse Experience Reporting		X	X	X	X	X		X	X
Assess for exposure to varicella or HZ ^{¶¶}			X	X	X	X			
End of Study Questionnaire									X

†	Monthly efficacy contact by telephone, via the internet, or during a study visit will be required for each patient for the duration of the study to assess for occurrence of unreported symptoms of suspected HZ. At Visit 5, site personnel will assist the patient with the first efficacy contact using the IVRS via the internet or via phone.
‡	Beginning 3 months following Visit 5 and continuing every 3 months for the duration of the study, patients will be contacted by site personnel, and using a pre-defined script, patients will be queried as to whether all serious adverse experiences have been reported since last contact. Concomitant medications administered as a result of any SAE for the duration of the study will also be collected. Information obtained from this contact will facilitate accurate and timely reporting of SAEs
§	Study will continue until the required number of cases of herpes zoster (HZ) has accrued, or if the decision is made to terminate the study or one arm early following a recommendation made by the DMC based on safety concerns or futile efficacy results from the interim futility analysis or if the trial is declared infeasible. At that time, the study or arm will begin to enter the close-out phase and no additional suspected HZ cases will be accrued. Patients already entered in suspected HZ case follow-up will complete their 6-month HZ assessment period. In the event the study or arm is terminated sooner than 1 year after the last vaccine dose is administered in this study, the study will continue to allow all patients to complete a minimum of 1 year post-vaccination follow-up for safety and efficacy. All patients enrolled in the study will be contacted by telephone to complete the study close-out questions.
	The allowable window between each vaccine dose is 20 to 40 days. All study procedures must be performed at the vaccination visit. Visit window permitted for Visit 5 is 28 to 60 days Postdose 4. Every attempt should be made to schedule the patient's Postdose 4 follow-up visit as close to day 28 Postdose 4 to assure for accurate and timely safety reporting. Deviations from the permitted visit windows (i.e., the patient meets deferment criteria or the patient is not able to complete the visit as scheduled per protocol because of medical or logistical reasons) require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision on patient management.
¶	Women of childbearing potential must have serum or urine pregnancy testing (sensitive to 25IU β-hCG) at enrollment and prior to subsequent vaccination doses. See Section 2.2 (inclusion criterion #7) for a definition of "woman of childbearing potential" under this Protocol.
#	Study personnel will access IVRS to register patients visit at time of randomization and at subsequent visits. IVRS will assign V212 or placebo to the patient at the time of randomization and at subsequent dosing visits.
††	Blood samples (5 mL) will be collected from all patients in the STM study group (based on the planned number of ~2696 patients) and used for testing via gpELISA. Sample collection procedures are provided in the Laboratory Manual.
‡‡	Blood samples (60 mL) will be collected from all patients enrolled in the ELISPOT substudy and tested via IFN-γ ELISPOT. Sample collection procedures are provided in the Laboratory Manual.
§§	Patients will be instructed to record daily <u>oral</u> temperatures and injection-site and systemic adverse experiences on the VRC from the date of each vaccine dose through the day prior to the next dose, or for 28 days Postdose 4. The VRC actively prompts for reporting injection-site adverse experiences for 5 days after each vaccination dose.
	Collect information about adverse experiences. Patients must complete safety follow-up after each vaccination dose and record adverse experiences on the VRC. After each vaccination dose, a new safety follow-up should begin using a new VRC.
¶¶	Study personnel will obtain information detailing the patient's exposure to varicella and/or HZ since last visit. Exposure is defined as contact with an individual from 5 days prior to the onset of a chickenpox rash, or from the day of onset of an HZ rash, until crusting of lesions
IVRS = Interactive Voice Response System	
IFN-γ ELISPOT = Interferon-gamma enzyme-linked immunospot assay	
gpELISA = glycoprotein enzyme-linked immunosorbent assay	
VRC = Vaccination Report Card	
PCR = polymerase chain reaction	
<u>Note:</u> Patients who contact the site for rash or acute HZ symptom(s) evaluation should be seen by a medically qualified investigator as soon as possible, preferably within 24 to 72 hours of rash or symptom(s) onset and if they have a suspected case of HZ, will be monitored for 6 months of HZ follow-up. For additional information, see "Study Flow Chart for Patients with Suspected HZ" in Section 1.8.	

1.8 STUDY FLOW CHART FOR PATIENTS WITH SUSPECTED HZ

	Onset of rash or other symptoms of HZ	First Evaluation [†]	Every 3 to 5 days until no new lesions appear/acute HZ symptom(s) improve	1 month post-symptom onset	2 months post-symptom onset	3 months post-symptom onset	4 months post-symptom onset	5 months post-symptom onset	6 months post-symptom onset
Visit window permitted (days) [‡]	N/A	N/A	N/A	(+/-5 days)	(+/-5 days)	(+/-5 days)	(+/-5 days)	(+/-5 days)	(+/-5 days)
Patient calls site	X								
Perform assessment of HZ rash, acute HZ-related symptom(s) and HZ-related complications [§]		X	X						
Collect lesion sample for PCR (for patients with an HZ-like RASH)		X							
Collect blood sample for PCR (for all patients with suspected HZ) [‡]		X							
Assess for exposure to varicella or HZ [#]		X							
Perform ZBPI assessment ^{††}		X	X	X	X	X	X	X	X
Perform EuroQol-EQ5D assessment ^{‡‡}		X	X	X	X	X	X	X	X
Perform HCU assessment ^{§§}		X	X	X	X	X	X	X	X
Perform WPQ assessment		X	X	X	X	X	X	X	X
[†] All patients who experience rash or other symptoms that could be due to a suspected case of HZ should be seen by a medically qualified investigator (defined as a physician, or in accordance with local regulations, a nurse practitioner or physician assistant) as soon as possible, preferably within 24 to 72 hours of rash onset. Antiviral therapy should be started and diagnostic procedures should be performed as soon as possible after HZ symptom onset. Report all concomitant medications (i.e., antiviral treatment, pain medications) administered as a result of a suspected case of HZ for the duration of the study. [‡] Study procedures may be performed up to 5 days prior or 5 days following the scheduled visit day. Deviations from the permitted visit windows (i.e., if the patient will not be able to complete visit as scheduled per protocol because of medical or logistical reasons) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on patient management. [§] For suspected HZ cases with rash, patients should be monitored by a medically qualified investigator for rash evolution and the signs and symptoms of the development of HZ-associated complications every 3 to 5 days until no new skin lesions appear, and clinical findings and relevant laboratory results should be reported. For suspected HZ cases without a rash, patients should be monitored by a physician for acute HZ progression and the signs and symptoms of the development of HZ-associated complications every 3 to 5 days until acute HZ symptoms are resolved, and clinical findings and relevant laboratory or radiologic results should be reported. Skin lesion samples will be collected for analysis by PCR for patients with an HZ-like rash. If the patient develops a suspicious rash after the first evaluation for a suspected case of HZ, the skin lesion samples for PCR should be obtained when the rash is first observed.									

[¶] All patients with suspected HZ will have two 10-mL whole blood samples collected for analysis by PCR at the initial evaluation only. Sample collection procedures are provided in the Laboratory Manual.

[#] Study personnel will obtain information detailing the patient's exposure to varicella and/or HZ since vaccination. Exposure is defined as contact with an individual from 5 days prior to the onset of a chickenpox rash, or from the day of onset of an HZ rash, until crusting of lesions.

^{††} Severity of pain and interference with activities of daily living (ADL) will be assessed using the Zoster Brief Pain Inventory (ZBPI) at each evaluation time point.

^{**} Functional health status and quality of life will be assessed using the European Quality of Life (EuroQol-EQ5D) questionnaire.

^{§§} HZ-related non-protocol-mandated health care resource utilization will be assessed using the Health Care Utilization (HCU) questionnaire.

^{||} Work and productivity loss will be assessed using the Work Productivity Questionnaire (WPQ).

HZ = Herpes Zoster
PCR = polymerase chain reaction
IVRS = Interactive Voice Response System

Note: After no new lesions appear or when acute HZ symptom(s) improve all assessments will be obtained (by telephone or during a study visit) for 6 months from onset of suspected HZ.

Note: Patients with a suspected case of HZ who have pain persisting longer than 6 months should continue in HZ follow-up until the pain resolves or the study ends.

Note: Deviations from the 6-month suspected HZ case follow-up period as scheduled per protocol because of medical or logistical reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary Objectives

1. To assess the safety and tolerability of V212 when administered to adults with STM .
2. To assess the impact of V212 on the development of HZ in adults with STM.

2.1.2 Primary Hypotheses

Vaccination with V212 will reduce the incidence of HZ compared with placebo in adults with STM. The following hypothesis will be tested at the end of the study in the STM population.

- 1) The statistical criterion for success requires that the lower bound of the 97.5% (one-sided $\alpha=0.0125$) confidence interval (CI) for the estimated vaccine efficacy in adults with STM be greater than 25%.

2.1.3 Secondary Objectives

1. To assess the impact of V212 on the development of moderate to severe HZ-associated pain at any time from HZ onset through the end of the 6 month HZ follow-up period. Moderate to severe HZ-associated pain is defined as 2 or more occurrences of a score of 3 or greater (0-to-10 scale) on the Zoster Brief Pain Inventory (ZBPI).
2. To assess the impact of V212 on the development of HZ complications defined as the occurrence of any of the following during the study: hospitalization or prolongation of hospitalization due to HZ, disseminated HZ (including disseminated HZ rash or VZV viremia), visceral HZ, ophthalmic HZ, neurological impairment due to HZ, or administration of intravenous acyclovir therapy for treatment of HZ.
3. To assess the impact of V212 on the development of PHN. PHN is defined as a worst pain score (in the previous 24 hours) of 3 or greater (0-to-10 scale) on the ZBPI, that persists or appears greater than or equal to 90 days after the onset of HZ rash.

The above objectives will be evaluated for STM only.

2.1.4 Exploratory Objectives

1. To assess the safety and tolerability of V212 when administered to adults with HM.
2. To assess the impact of V212 on the development of HZ in adults with HM.
3. To assess the impact of V212 on the development of moderate to severe HZ-associated pain at any time from HZ onset through the end of the 6 month HZ follow-up period. Moderate to severe HZ-associated pain is defined as 2 or more occurrences of a score of 3 or greater (0-to-10 scale) on the Zoster Brief Pain Inventory (ZBPI) in adults with HM.

4. To assess the impact of V212 on the development of HZ complications defined as the occurrence of any of the following during the study: hospitalization or prolongation of hospitalization due to HZ, disseminated HZ (including disseminated HZ rash or VZV viremia), visceral HZ, ophthalmic HZ, neurological impairment due to HZ, or administration of intravenous acyclovir therapy for treatment of HZ in adults with HM.
5. To assess the impact of V212 on the development of PHN. PHN is defined as a worst pain score (in the previous 24 hours) of 3 or greater (0-to-10 scale) on the ZBPI, that persists or appears greater than or equal to 90 days after the onset of HZ rash in adults with HM.
6. To assess the immunogenicity of V212 in adults with STM or HM.
7. To describe the impact of HZ on activities of daily living (ADL) and quality of life (QoL), and to assess the impact of V212 on interference with ADL and QoL in study patients who develop HZ.
8. To describe HZ-related non-protocol-mandated health care resource utilization (HCRU), and assess the impact of V212 on HZ-related non-protocol-mandated HCRU, and work and productivity loss (WPQ).
9. To assess the impact of V212 on the severity and duration of HZ-related pain.
10. To assess the impact of V212 on the severity of HZ rash including the extent of rash, number of skin lesions present, and number of dermatomes involved.
11. To assess the association of immunogenicity at postvaccination with the risk of HZ in adults with STM or HM.

The exploratory objectives (1)-(5) will be evaluated for HM only; objectives(6)-(10) will be evaluated for STM and HM separately and (11) will be evaluated in both combined STM and HM populations and individual subpopulation.

2.2 PATIENT INCLUSION CRITERIA

An individual will be eligible to participate in this study if all of the following criteria apply:

1. Patient has been diagnosed with a solid tumor or hematologic malignancy AND is not likely to undergo hematopoietic cell transplant (HCT) and meets one of the criteria specified below.
 - Is 18 years of age or older and is receiving a cytotoxic or immunosuppressive chemotherapy regimen.

OR

- Is 50 years of age or older* with a hematologic malignancy, not in remission, regardless of whether the patient is or is not receiving chemotherapy.

* **Note: In India only, enrollment is restricted to patients 18 to 65 years of age.**

2. Life expectancy \geq 12 months.
3. Signed an informed consent prior to any study procedures.
4. Patient has prior history of varicella, antibodies to VZV (documented prior to receipt of blood products), or residence (for \geq 30 years) in a country with endemic VZV infection, or if participant is <30 years old, attended primary or secondary school in a country with endemic VZV infection (see Section 3.2.8 for more details).
5. All female patients of childbearing potential (as defined below under #7) must have a negative serum or urine pregnancy test (sensitive to 25IU β -hCG).
6. Able to understand and complete study questionnaires.
7. Patient is highly unlikely to conceive during the time period starting 2 weeks prior to enrollment through 6 months from last vaccination dose, as indicated by at least one “yes” answer to the following questions:
 - Patient is male.
 - Patient is female who agrees to remain abstinent or use (or have their partner use) adequate contraception during the time period starting 2 weeks prior to enrollment through 6 months from the last vaccination dose. Note that simultaneous use of two reliable forms of contraception is recommended.
 - Patient is a female who is not of reproductive potential. A female patient who is not of reproductive potential is defined as: one who has either (1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle stimulating hormone [FSH] levels in the postmenopausal range as determined by a laboratory, or 12 months of spontaneous amenorrhea), (2) post-surgical bilateral oophorectomy and/or hysterectomy, or (3) bilateral tubal ligation.
8. Patients with STM will be eligible for enrollment if they have not received (nor are expected to require receipt of) blood products within 3 months prior to enrollment through 28 days Postvaccination 4.

2.3 PATIENT EXCLUSION CRITERIA

An individual will not be eligible to participate in this study if any of the following criteria apply:

1. A history of allergic reaction to any vaccine component (including gelatin) or an anaphylactic/anaphylactoid reaction to neomycin (a history of contact dermatitis to neomycin is not a criterion for study exclusion).
2. Prior history of HZ within 1 year of enrollment.
3. Prior or expected receipt of any varicella or non-study zoster vaccine.
4. Patient is currently receiving or expected to receive long-term antiviral prophylaxis (greater than 4 weeks duration) with activity against herpes simplex virus (HSV), VZV or cytomegalovirus (CMV).
5. Patient is pregnant or breastfeeding or expecting to conceive within the period of 2 weeks prior to enrollment throughout 6 months after last vaccination dose.
6. Any live virus vaccine administered or scheduled in the period from 4 weeks prior to Dose 1 through 28 days postvaccination dose 4.
7. Any inactivated vaccine administered or scheduled within the period from 7 days prior to, through 7 days following, any dose of study vaccine.
8. Unlikely to adhere to the study procedures or attend study visits.
9. Any other reason that in the opinion of the investigator might interfere with the evaluation required by the study.
10. Patients with STM will be excluded from study if they have received (or are expected to require receipt of) blood products within 3 months prior to enrollment through 28 days Postvaccination 4.

2.3.1 Deferment Criteria (Prior to Vaccination of Doses 2 through 4)

NOTE: SPONSOR must be notified of deferment. At sites located in the United States, site personnel should contact one of the study personnel listed on the Sponsor Contact page in the Administrative Binder. Internationally, the site should contact the local Merck subsidiary monitor.

1. The patient has an acute illness that requires active medical intervention or monitoring to avert serious danger to the participant's health or well-being and, in the opinion of the investigator, may interfere with the evaluation of the study objectives. (The maximum amount of time for which the vaccination should be deferred is 30 additional days).

2. The patient has received an inactivated vaccine such as the influenza vaccine. In that case, administration of the study vaccination should be deferred for 7 days following receipt of the inactivated vaccine.

The deferment criteria noted above must be reviewed prior to each vaccination for Doses 2 through 4, to ensure that patients do not meet the criteria specified. If a participant meets any deferment criterion, this must be reported to the SPONSOR, and all study procedures with the exception of the administration of the vaccine/placebo should be conducted on the day the vaccination was deferred.

2.3.2 Continuation in the Study under Special Circumstances

A patient should not receive additional doses of vaccine or placebo but should remain in the study to be followed for safety, efficacy and immunogenicity if:

- The patient develops a severe allergic reaction to a component of the vaccine (i.e., swelling of the mouth and throat, difficulty breathing, hypotension or shock) following administration of the prior vaccine dose.
- The patient becomes pregnant.
- The patient undergoes hematopoietic cell transplant (HCT).

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a randomized, double-blind (with in-house blinding procedures), placebo-controlled, multicenter study to evaluate the efficacy, immunogenicity, safety and tolerability of V212 in adults with STM or HM. The study will enroll patients who are 18 years of age and older who have either STM or HM and are receiving chemotherapy. **(Note: In India only, enrollment is restricted to patients 18 to 65 years of age.)** In addition, patients 50 years of age and older who have HM, not in remission, will be enrolled regardless of whether they are receiving chemotherapy. **(Note: In India only, patients 50 to 65 years of age who have HM, not in remission, will be enrolled regardless of whether they are receiving chemotherapy.)**

Approximately 5264 patients (~2632 in the vaccine group; ~2632 in the placebo group), 18 years of age or older will be randomized to receive either V212 or placebo given as a 4-dose regimen administered ~30 days apart. **(Note: In India only, enrollment is restricted to patients 18 to 65 years of age.)** Randomization will be stratified by baseline medical condition with approximately 2696 patients with STM (receiving chemotherapy) and 2568 patients with HM enrolled into the study. Patients with HM will be further stratified into one of two strata, low immunocompromise (IC) or moderate to high IC, based on the patient's HM diagnosis and/or chemotherapeutic regimen (see Appendix 6.1). The planned randomization schedule by vaccination group is shown in Section 2.4.2. Enrollment for this study is expected to be completed in approximately 36 months.

This is an event-driven study based upon the occurrence of confirmed HZ cases. The combined dropout rates and the combined HZ event rates will be monitored on an ongoing basis using the blinded database. Patients will remain in the study from the time of enrollment until accrual of the targeted number (~90) of confirmed HZ cases in the STM population.

The planned study duration stated in this protocol is estimated based upon assumptions related to enrollment rate and follow-up time and HZ incidence in these populations. If these assumptions are met, the study will continue for approximately 5 years in order to accrue approximately 90 confirmed HZ cases. However, it should be noted that:

- Study duration may be less than or more than 5 years, depending upon the time it takes to accrue the necessary number of confirmed cases.
- The HZ event rates will be monitored on an ongoing basis using the blinded database. If the observed HZ case accrual rate indicates that more than 5 years of patient follow-up will be necessary to accrue the targeted number of confirmed cases, then the SPONSOR will declare the trial infeasible and terminate the study after approximately 5 years of patient follow-up have occurred, from the date the first patient is enrolled.

This study will use an adaptive design based on pre-specified vaccine efficacy criteria, using an independent, external DMC. There will be one interim analysis and one final efficacy analysis. The interim analysis will consist of a futility analysis for each individual subgroup (HM and STM).

The interim (futility) analysis was conducted when at least 50% of the total number of required confirmed HZ cases had accrued in each patient population, HM and STM. The interim analysis was conducted on 29-Oct-2014 for both populations. Results of the analysis were reviewed by the DMC, who made recommendations to the Steering Committee (SC) to end the study in the HM population and continue the STM arm only.

Patients will be monitored for HZ for the entire duration of the study. To that end, patients will be educated on the signs and symptoms of HZ and instructed to call the study site immediately if such symptoms develop, to arrange an evaluation by a medically qualified investigator (medically qualified is defined as physician, or in accordance with local regulations, a nurse practitioner or physician assistant). In addition, monthly efficacy contact by telephone, via the internet, or during a follow-up visit will be required for each patient until study completion, to determine if unreported HZ symptoms occurred.

It is important to note that HZ presentation in immunocompromised patients may be atypical, for instance with cases of rash over several dermatomes. Also, occurrence of severe complications is not uncommon. Finally, visceral involvement is possible and HZ can occur without a rash. In such cases, detection of VZV in diagnostic specimens from blood, cerebrospinal fluid (CSF), lung, liver or other organ may be a key element of the diagnosis of HZ. More information about identification of suspected HZ cases can be found in Section 3.2.17.2.

The follow-up of patients with suspected HZ (outlined in the flowchart in Section 1.8) will include the following steps:

- *Initial evaluation by a medically qualified investigator* – All patients with suspected HZ will be assessed by a medically qualified investigator as soon as possible after HZ symptom onset. During this first evaluation, samples for VZV PCR testing will be collected from skin lesions in patients with a HZ or HZ-like rash. In addition, blood samples for VZV PCR testing will be collected from all patients.
- *Continued monitoring by a medically qualified investigator until no new lesions or symptoms of HZ appear* – Patients will be subsequently assessed every 3-5 days by a medically qualified investigator until no new lesions appear and no new acute HZ symptoms appear. Subjects with a rash should be assessed for rash evolution and the signs and symptoms of the development of HZ-associated complications, and any relevant laboratory findings should be reported. For subjects without a rash, clinical findings and any relevant laboratory and radiologic results should be reported. Severity of HZ-related pain, the development of HZ-associated complications, interference with activities of daily living, functional health status, quality of life, HZ-related healthcare utilization and effect on work/productivity will be assessed through the use of interview questionnaires administered by site personnel.

Monthly follow-up assessment over a 6-month period – Patients will also undergo serial (monthly) assessments over the 6 months following the initial report of suspected-HZ to capture the progression and resolution of disease characteristics such as severity of HZ-related pain, the development of HZ-associated complications, interference with activities of daily living, functional health status, quality of life, HZ-related healthcare utilization and effect on work/productivity. These assessments will be conducted through the use of interview questionnaires administered by site personnel (WPQ, HCU), or completed by the patient (ZBPI, European Quality of Life [EurQoL/EQ5D]) as indicated. Patients with a suspected case of HZ who have pain persisting longer than 6 months should continue in HZ follow-up until the pain resolves or the study ends.

The summary of clinical findings, including any results of non-study laboratory and radiologic assessments conducted locally to support the HZ diagnosis, and results from the blood VZV PCR testing will be provided to the Clinical Adjudication Committee (CAC).

Another important goal of the study is to evaluate the safety and tolerability of V212 in the HM and STM patient populations. Adverse experiences will be collected from Visit 1 through Visit 5 using a Vaccination Report card (VRC). All subjects will receive a VRC at each vaccination visit (Visits 1 through 4). The VRC will be used to collect safety information between each vaccination period (minimum 20 days postvaccination dose 1 through 3, through 28 days postvaccination dose 4). The VRC will be returned by the patient and reviewed by study site personnel at the next scheduled study visit.

Serious adverse experiences (SAE) will be collected, regardless of causality, for the entire duration of the study. Patients will be instructed to call the study site immediately, at any time during the study, if they develop an adverse experience that meets SAE criteria. In addition patients undergo periodic safety follow-up to assess whether they developed a clinical adverse experience that met SAE criteria since their last contact with site personnel. As indicated in the Study Flow Chart (Section 1.7), such safety follow-ups will occur at each scheduled study visit (Visit 1 through 5) and, after Visit 5, by telephone Periodic Safety Contact (approximately every 3 months, beginning 3 months following Visit 5, and continuing every 3 months for the duration of the study).

A pregnancy test will be performed on all female patients of childbearing potential at Visits 1, 2, 3, and 4 prior to vaccine administration. Any female patient with a positive pregnancy test at Visit 1 will not be vaccinated and will not be allowed to participate in the study. Female patients with a positive pregnancy test after Visit 1 will not receive additional doses of V212 or placebo, but will remain in the study to be followed for safety, efficacy and immunogenicity.

To ensure that no alarming, unusual, or unexpected safety problems are occurring with the vaccine in the HM or STM populations, safety will be monitored during the study by the same independent, external DMC that will monitor the interim futility and efficacy analyses. The DMC will periodically evaluate interim safety and efficacy data and will provide periodic recommendations to the SC, to continue, modify, or stop the clinical trial. See section 3.2.21 for more details about the DMC and SC.

Overall, the study may be ended in the following situations:

- 1) When the required number of confirmed HZ cases has accrued; or
- 2) If the decision is made to end the study early following a recommendation made by the DMC based on safety concerns; or
- 3) If the observed HZ case accrual rate indicates that more than 5 years of patient follow-up will be necessary to accrue the targeted number of confirmed cases, then the SPONSOR will declare the trial infeasible and terminate the study after approximately 5 years of patient follow-up have occurred, from the date the first patient is enrolled

In any of these situations, the study will begin to enter the close-out phase, and no additional suspected cases of HZ will be accrued beyond the date for initiation of close-out procedures, as provided in the Close-Out Standard Operating Procedures (SOP) and patients already entered into the suspected HZ-follow-up will complete their 6-month assessment periods. All patients will be contacted to complete the study close-out questionnaire. Details of the close-out procedures will be provided in the Close-Out SOP. In the event the study ends sooner than 1 year after the last vaccine dose is administered, the study will continue to follow all patients for safety and efficacy until all patients have completed 1 year of follow-up.

The clinical, statistical and data management study personnel at the SPONSOR who are involved with study conduct will remain blinded to subject vaccination group allocations until the required number of cases of the primary efficacy endpoint have been observed, study close-out procedures have been completed, data discrepancies have been addressed, and the database is unblinded for the primary efficacy analysis.

2.4.2 Vaccination Plan

Approximately 5264 patients (~2632 vaccine recipients; ~2632 placebo recipients), 18 years of age or older will be randomized 1:1 to receive either V212 or placebo given as a 4-dose regimen approximately 30 days apart. (**Note: In India only, enrollment is restricted to patients 18 to 65 years of age.**) Each dose of V212 or placebo will be administered as a 0.5-mL subcutaneous injection preferably in the deltoid region of the arm, alternating arms for each V212 or placebo dose, if possible. Placebo will be the vaccine stabilizer for V212 with no virus antigen.

Randomization will be stratified by disease type (i.e., HM or STM) with approximately 2696 patients with STM (receiving chemotherapy) and approximately 2568 patients with HM enrolled into the study. Patients with HM will be further stratified into one of two strata, low IC or moderate to high IC (see Appendix 6.1). Randomization and stratification will be based upon a randomization schedule generated by the SPONSOR. The planned randomization schedule by vaccination group is shown in [Table 2-1](#).

Table 2-1

Randomization Schedule

Vaccination Group	Stratification		
	STM	HM [‡]	Total
V212	1348	1284	2632
Placebo	1348	1284	2632
Total	2696	2568	5264
[‡] HM population will be further stratified into one of two strata, low IC or moderate to high IC which is expected to be in 1:3 ratio approximately.			

An Interactive Voice Response System (IVRS) will be used to register patient visits upon randomization and at subsequent visits. The IVRS will be used to allocate patients to vaccination group assignments during randomization according to a central randomization schedule generated by the SPONSOR. For all sites, all vaccine doses will be shipped through the IVRS.

2.5 LIST OF EFFICACY/IMMUNOGENICITY MEASUREMENTS

2.5.1 HZ Case Determination

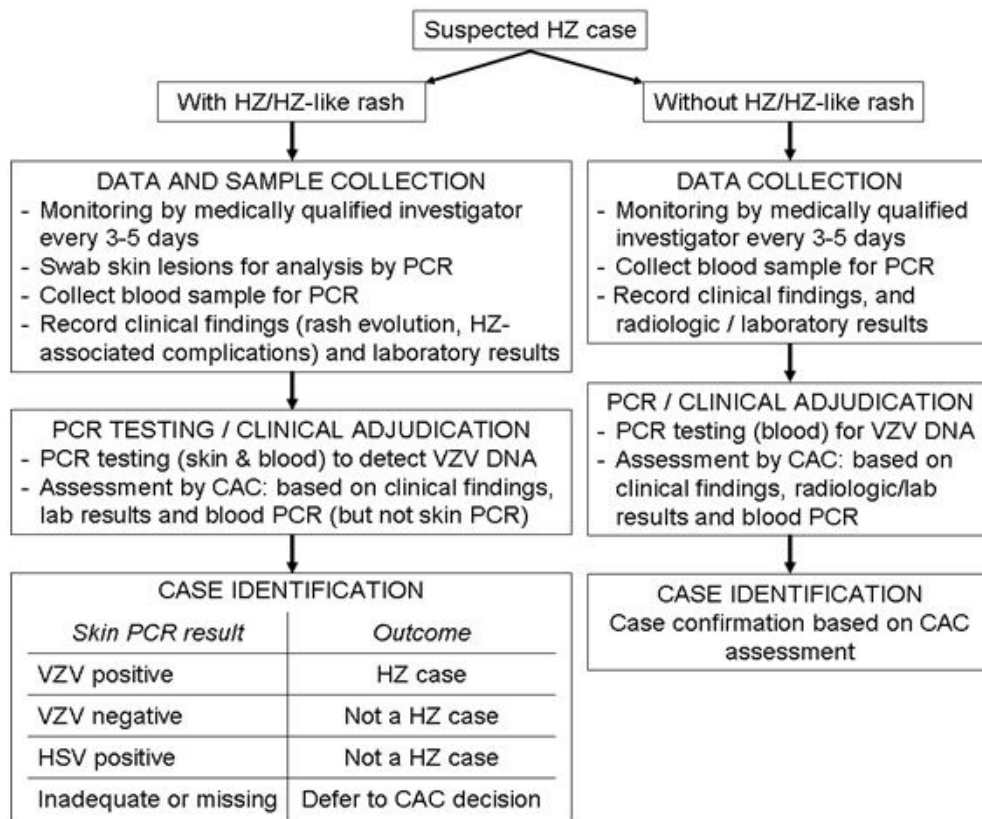
The primary clinical efficacy endpoint will be the incidence of HZ. Clinical criteria for suspected HZ cases are the development of a papular or vesicular rash with a dermatomal or generalized distribution, or in the absence of a rash, clinical suspicion of VZV infection with or without the detection of VZV in diagnostic specimens from blood, CSF, lung, liver, or other organ. In immunocompromised patients, the rash of HZ may be atypical, for example involving more than one dermatome, or it may not be present. Patients who develop suspected HZ will enter 6 months of HZ follow-up.

All suspected cases of HZ will go through case adjudication in a blinded fashion by the CAC. The CAC will determine if a suspected case is a confirmed case of HZ, in their clinical opinion, and if a confirmed case make the final determination of the confirmed HZ complication(s) present. HZ case determination will be based primarily upon the results of the skin lesion PCR assay, if applicable. For those cases that do not include a skin lesion PCR assay or if the skin PCR assay is inadequate, case confirmation will be based on the result of adjudication of the clinical case description by the CAC, conducted according to the CAC SOP.

The algorithm used for determination of HZ cases is shown in [Figure 2-1](#). PCR assays for the detection of VZV DNA will be conducted as described in Section 3.3. The summary of clinical findings, laboratory and radiologic results, and results from the blood VZV PCR will be provided to the CAC.

Figure 2-1

HZ Case Determination



2.5.2 Secondary Efficacy Measurements

Three secondary efficacy endpoints are defined for this protocol which will be evaluated in the STM population only and in the HM population on an exploratory basis. The first is to assess the incidence of moderate to severe HZ-associated pain [defined as 2 or more occurrences of a score 3 or greater (0-to-10 scale) in response to the prompt to rate "your pain at its worst in the last 24 hours" on the ZBPI, at any time from HZ onset through the end of the 6 month HZ-follow-up period. The second is a composite efficacy endpoint of the incidence of HZ complications, defined as the occurrence of any of the following during the study: hospitalization or prolongation of hospitalization due to HZ, disseminated HZ (including disseminated HZ rash or VZV viremia), visceral HZ, ophthalmic HZ, neurological impairment due to HZ, or administration of intravenous acyclovir therapy for treatment of HZ. The third endpoint is the incidence of PHN [defined as a worst pain score (in the last 24 hours) of 3 or greater (0-to-10 scale) in response to the prompt to rate "your pain at its worst in the last 24 hours" on the ZBPI, that persists or appears greater than or equal to 90 days after the onset of the HZ rash].

The CAC will determine whether HZ complications have occurred based on the clinical findings, laboratory and radiologic results from subjects with suspected HZ cases, as well as results from the blood VZV PCR testing.

2.5.3 Immunogenicity Measurements

The study will provide an exploratory immunogenicity assessment of V212, as shown in Table 2-2. The goal is to assess the immunogenicity of the vaccine and to attempt to demonstrate correlation of immune responses to the vaccine with clinical efficacy. Serum VZV antibody levels will be measured by gpELISA in patients in the STM study group. Serum samples will be collected on Day 1/Visit 1 (prior to Dose 1) and Visit 5 (~28 days Postdose 4) based on the original enrollment plan (~2696 patients).

A subset of the study population will be enrolled in an ELISPOT substudy to measure T cell response by IFN- γ ELISPOT. Peripheral blood mononuclear cells (PBMC) will be collected from those enrolled in the ELISPOT substudy (n ~ 1000), on Day 1/Visit 1 (prior to Dose 1) and Visit 5 (~28 days Postdose 4). Participation in the ELISPOT substudy will be limited to select sites based upon accessibility to PBMC processing laboratories. At these sites, the first 500 patients enrolled in the STM group and the first 500 enrolled in the HM group will be enrolled in the ELISPOT substudy.

Patients enrolled in the ELISPOT substudy will have a separate allocation schedule to assure a well-balanced randomization ratio. All investigative sites participating in the ELISPOT substudy will enroll each consented patient into the ELISPOT substudy until the target enrollment of 1000 patients has been met.

Table 2-2

Exploratory Immunogenicity Assessment of V212

Assay	Goal	Population
gpELISA	Assess T cell-dependent antibody response	<ul style="list-style-type: none">• STM = ~2696 patients• HM = none
IFN- γ ELISPOT	Assess T cell response	<ul style="list-style-type: none">• STM = ~500 patients*• HM = ~500 patients*
* Limited to select sites with adequate laboratory processing capabilities		

2.6 LIST OF SAFETY MEASUREMENTS

The safety evaluation will focus on the clinical safety and tolerability profile following all 4 vaccine doses. In addition, SAE will be collected for the entire duration of the study regardless of causality.

All subjects will receive a VRC at each vaccination visit (Visits 1 through 4). On the VRC, patients will be asked to record daily oral temperature measurement, local and systemic adverse experiences, as well as concomitant medications, and non-study vaccinations. In addition, patients will be actively prompted to record on the VRC, injection-site adverse experiences for 5 days following each vaccination dose, exposure to varicella or HZ, and development of varicella/varicella-like or HZ/HZ-like rash. Patients will receive a new VRC for each dose of vaccine/placebo. The VRC will be used by the patients to collect safety information between each vaccination period (minimum 20 days postvaccination dose 1 through 3, through 28 days postvaccination dose 4). The VRC will be reviewed by study site personnel at the end of the minimum 20-day follow-up period following each V212 or placebo dose.

SAE will be collected as follows. Patients will be instructed to call the site immediately, at any time during the study, if they experience a clinical adverse experience that results in a hospitalization, prolongs a hospitalization, is a cancer or an overdose, or is another severe, unexpected, life-threatening event that could potentially be considered serious (see section 3.4.6 for a complete definition of a SAE). An SAE that is a worsening of a pre-existing condition should also be reported. Patients will also be asked, either at a scheduled study visit (Visit 1 through 5) or, after Visit 5, by telephone Periodic Safety Contact (approximately every 3 months, starting approximately 3 months following Visit 5), whether they developed a clinical adverse experience that met SAE criteria since the last contact with site personnel. Using a pre-specified script (developed by the SPONSOR) that enables the collection of relevant information related to an SAE, site personnel will query the patient and record the patient's responses to facilitate reporting of the event.

As described in Section 3.4.1.3, toxicity grading will be applied for all serious and non-SAEs in this study based on a toxicity grading scale. This is in addition to the grading of adverse experiences by maximum intensity described in Table 3-1.

Pregnancy information will be collected as described in Section 3.4.4.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.5 of protocol details.

2.7.1 Efficacy

The primary efficacy endpoint is the incidence of HZ in the vaccine and placebo groups in the STM population, defined as the number of HZ cases per 1000 person-years of follow-up from study enrollment to the end of study. Vaccine efficacy for HZ (VE_{HZ}) is defined as the relative reduction of the hazard rate of HZ in the V212 group compared with that in the placebo group. The primary statistical hypothesis for the primary efficacy is $H_0: VE_{HZ} \leq 25\%$ versus $H_1: VE_{HZ} > 25\%$.

Appropriate multiplicity adjustment will be made for the planned interim analyses. The primary analysis will be based on a modified intent-to-treat (MITT) population, defined as all randomized patients who received at least one dose of the vaccination. The hypothesis test and corresponding CI will be based on a Cox proportional hazards regression model stratified by age (< 50 years of age versus ≥ 50 years of age).

Three secondary efficacy endpoints are defined for STM population. The three secondary efficacy endpoints are defined as follows: (1) incidence of moderate to severe HZ-associated pain (defined as 2 or more occurrences of a score of 3 or greater (0-to-10 scale) in response to the prompt to rate "your pain at its worst in the last 24 hours" on the ZBPI), at any time from HZ onset through the end of the 6 month HZ-follow-up period. (2) composite efficacy endpoint of the incidence of HZ complications during the study, defined as the occurrence of any of the following during the study: hospitalization or prolongation of hospitalization due to HZ, disseminated HZ (including disseminated HZ rash or VZV viremia), visceral HZ, ophthalmic HZ, neurological impairment due to HZ, or administration of intravenous acyclovir therapy for treatment of HZ. (3) the incidence of PHN (defined as a worst pain score [in the last 24 hours] of 3 or greater [0-to-10 scale] in response to the prompt to rate "your pain at its worst in the last 24 hours" on the ZBPI that persists or appears greater than or equal to 90 days after the onset of the HZ rash). A Cox proportional hazards regression model will be fitted for each of these three secondary endpoints stratified by age (< 50 years of age versus ≥ 50 years of age).

Additional supportive and exploratory efficacy analyses including safety and tolerability assessment and the impact of V212 on the development of HZ in the HM population, and the vaccine efficacy durability, other HZ-associated complications, the severity and duration of HZ-related pain and the interference on activities of daily living (ADL tool), Quality of Life (EuroQoL/EQ5D tool) and healthcare utilization (HCU tool) will also be provided for the HM and STM populations separately.

2.7.2 Immunogenicity

All immunogenicity analyses in this study are exploratory. All patients in the STM study group will have serum samples collected at Day 1/Visit 1 and at Visit 5 (~28 days postvaccination dose 4) to assess a T-cell dependent antibody response by gpELISA. In addition, a subset of study patients (n ~ 1000) in both the STM and HM populations will participate in the ELISPOT substudy and undergo testing for VZV T-cell responses by IFN- γ ELISPOT assay. The geometric mean titer (GMT) or geometric mean count (GMC) and geometric mean fold rises (GMFR) for both the gpELISA and ELISPOT will be provided by vaccination group at scheduled time points (see Section 1.7) for the HM and STM populations separately. A longitudinal regression model will be used to estimate the fold difference at these time points between the vaccination groups, while adjusting for the prevaccination titers (see Section 3.5.5.2) for the HM and STM populations separately. Other exploratory analyses will also be performed to determine whether these VZV-specific immune responses are associated with protection against HZ using Cox proportional hazards models in the combined STM and HM populations.

2.7.3 Safety

Patients will be followed for safety for the duration of the study. In the event study close-out begins prior to all patients on study completing the required 1 year of follow-up from the time of the last vaccination dose, the study will continue to allow all patients to complete the required 1 year of follow-up. Safety and tolerability of V212 will be assessed by evaluation of all relevant safety parameters for the HM and STM populations separately. The primary safety endpoint of the study will be based on the incidence of SAE observed during the period up to 28 days Postdose 4 in each vaccination group for the STM population. Two-sided 95% CI on the proportion of any vaccine-related SAE will be provided for each vaccination group based on the exact binomial distribution [19]. The risk difference on SAE between the two groups and the corresponding two-sided 95% CI on the risk difference will also be provided using the stratified asymptotic methods proposed by Miettinen and Nurminen [20].

Other key safety evaluations will include summaries of the proportions of patients reporting the following adverse experiences: 1) systemic adverse experiences prompted for on the VRC, including varicella-like rash and HZ-like rash, occurring from Day 1 to Day 28 after any study vaccination, 2) injection-site complaints prompted for on the VRC, such as redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 after any vaccination, 3) elevated temperature ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$] oral or oral equivalent), from Day 1 to Day 28 after any study vaccination. The risk differences between the two vaccination groups, corresponding two-sided 95% CI on the risk difference, and the p-value for the test of significant risk difference will be provided using an asymptotic method for differences of 2 independent binomial proportions adjusting for stratification factors.

The rate of SAEs, vaccine-related SAEs and death that occur throughout the entire study follow-up period will also be summarized per 1000 person-years of follow-up by vaccination group. Additional safety summaries including SAEs, vaccine-related SAEs and death will be provided in each vaccination group for the HM and STM populations separately.

2.7.4 Power and Sample Size

This is an event-driven study. With a 1:1 randomization ratio between the vaccine and placebo groups and a total of 90 HZ cases in the STM population with 2696 patients, the study will have an overall power of ~84.2% to detect 65% VE_{HZ} at the overall two-sided 0.025 significance level, based on the success criterion of the lower bound 97.5% CI for VE_{HZ} being greater than 25%.

To accrue ~90 confirmed HZ cases in the STM population during the time period from enrollment through approximately the end of maximum 5 years postvaccination, enrollment of approximately 2696 patients (1348 receiving vaccine and 1348 receiving placebo) will be required, assuming 1) 30% total lost-to-follow-up, 2) an HZ rate of 17 per 1000 in the placebo group for STM, 3) $\text{VE}_{\text{HZ}}=65\%$ for STM, and 4) 36 months of study enrollment. The sample size calculation follows the methods described in Lachin [21].

The dropout rates and the combined HZ event rates will be monitored on an ongoing basis using the blinded database. If ongoing blinded pooled event rate monitoring indicates that there may be fewer than 90 confirmed cases of HZ accrued for the STM population, then the follow-up time may be extended. More specifically, if the observed HZ case accrual rate indicates that more than 5 years of patient follow-up will be necessary to accrue the targeted number of confirmed cases, then the SPONSOR will consider it beyond the adjustment cap and terminate the study after 5 years of patient follow-up have occurred.

A subset of patients will participate in the ELISPOT substudy. Power and sample size of the ELISPOT substudy is discussed in Section 3.5.7.3.

2.7.5 Interim Analysis

The first interim analysis for futility was conducted on 29-Oct-2014. Text describing the analysis strategy can be found in Appendix 6.3.

3. PROTOCOL DETAILS

3.1 RATIONALE

3.1.1 General Background

HZ, commonly known as shingles or zoster, is a manifestation of the reactivation of VZV, which as a primary infection, produces chickenpox (varicella). Following initial infection, the virus remains latent in the dorsal root or cranial sensory ganglia, until it reactivates, producing HZ. HZ is usually characterized by a unilateral, painful, vesicular cutaneous eruption with a dermatomal distribution. MRL developed ZOSTAVAX™ for the prevention of HZ and its complications, especially HZ-related pain and PHN, in immunocompetent older adults.

Immunocompromised patients have a higher incidence of HZ, compared to the general population, and are at increased risk for developing severe and life-threatening complications as well as severely disabling PHN [2-12]. In the immunocompromised population, the clinical presentation of HZ may be atypical and nonspecific, and include signs and symptoms such as fever, abdominal pain, altered mental status and respiratory symptoms in the presence or absence of a cutaneous eruption. The incidence of HZ in such patients, including recipients of HCT and solid organ transplants, patients infected with HIV, patients on immunosuppressive therapies, and patients with autoimmune diseases such as systemic lupus erythematosus (SLE) ranges from 12 to over 50 cases per 1000 person-years, compared with an incidence of 7 to 11 per 1000 person-years in immunocompetent community-dwelling older adults [22-32].

Current treatment for HZ in immunocompromised hosts may include intravenous administration of acyclovir due to the high risk of severe morbidity and mortality associated with HZ in these patients. Antiviral therapy is most effective when given very early during the course of the disease.

The live, attenuated Oka/Merck varicella vaccine (VARIVAX™) has been studied in immunocompromised hosts in a variety of settings. Due to the documented risk of severe VZV-like rash and an increased rate of vaccine-related SAEs, reported in acute lymphoblastic leukemia (ALL) children who received VARIVAX™, which may result from replication of the vaccine virus strain in this setting, all of the live attenuated Oka/Merck VZV vaccines (VARIVAX™, ZOSTAVAX™ and ProQuad™) are contraindicated in patients with compromised immune systems [33].

The development of a suitable vaccine for the prevention and amelioration of HZ and HZ-related complications in immunocompromised persons would therefore address a significant unmet medical need in particularly vulnerable populations. Inactivation of the live attenuated Oka/Merck VZV vaccine by treatment with gamma-irradiation limits the quantity of live virus to a minimal level, while preserving the quantity of vaccine viral antigen, and therefore could be the basis for the development of a suitable vaccine.

3.1.1.1 Epidemiology of HZ in Patients with HM

In patients with HM, the incidence of HZ is significantly higher than that seen in the general population of the same age and that of immunocompetent older adults, and varies by the degree of immunosuppression caused by the underlying cancer diagnosis and treatments [22-30]. The incidence of HZ in Hodgkin's disease patients receiving chemotherapy was estimated to range from 50 to 70 per 1000 person-years within 3 years of follow-up [22-26]. For Non-Hodgkin lymphoma, HZ incidence was estimated to range from 25 to 50 per 1000 person-years over an average follow-up of 2 to 3 years [22, 24, 27, 28]. In patients with multiple myeloma, HZ incidence was estimated to range from 40 to 60 per 1000 person-years after 2 to 3 years of follow-up. The risk of HZ in multiple myeloma patients has been shown to significantly increase after treatment with bortezomib compared to no treatment or to high-dose dexamethasone [29, 30].

In a recent Merck-sponsored observational cohort study conducted at KPNC, a US managed care organization, in cancer patients with STM or HM diagnosed between 2001 and 2005, among ~2700 HM patients, the estimated incidence of HZ was 31 per 1000 person-years [13]. In this population, both the underlying cancer diagnosis and the treatment regimen resulted in immunosuppression. In this study, a consensus algorithm developed for database studies by immunology and infectious disease experts was used to classify the level of immunocompromise (IC) of patients into none/low, medium, or high. IC classification, updated on a monthly basis throughout the study period for each patient, was based on (1) the type of chemotherapy agents and/or corticosteroids used, (2) time since last chemotherapy/corticosteroid treatment, and (3) specific type of HM [31]. Corticosteroid therapy was classified into levels of IC based on dose and duration of treatment. Among HM patients, the incidences of HZ were 13, 25, and 48 per 1000 person-years in the low, moderate, and high IC groups respectively. The incidence of HZ was higher for patients who were receiving chemotherapy or corticosteroids during the study period (47 per 1000 person-years) than those who were not (17 per 1000 person-years). The incidences of HZ among patients with multiple myeloma, Hodgkin's lymphoma, non-Hodgkin lymphoma, and myeloid leukemia were 56, 51, 25, and 23 per 1000 person-years respectively. HZ can also be a significant source of morbidity in HM patients. The proportion of HZ cases complicated by PHN and disseminated zoster was estimated to range from ~5% to 33% and 5% to 19%, respectively [22-24, 28-29, 32-33]. In the KPNC study, among 140 incident HZ cases in the HM patients, approximately one in three patients (33.6%) developed at least one complication. PHN (zoster-associated pain persisting or appearing at or beyond 90 days post-HZ onset) occurred in 5.7% HZ cases. The proportion of cases with multiple dermatome involvement, skin-related, eye-related, or neurological complications was 7.9%, 19.3%, 3.6%, and 2.9% respectively.

3.1.1.2 Epidemiology of HZ in Patients with STM

Published data of HZ in the STM patient population are much more limited than for other IC populations. HZ incidence in this population was reported to range from 12 to 15 per 1000 person-years [33-39]. Aggressive and prolonged chemotherapy was widely identified as the primary factor for VZV reactivation [33-39]. In the KPNC study, the incidence of HZ among ~12,000 STM patients diagnosed during the study time period was 12 per 1000 person-years [13]. The incidence was 19, 20, and 10 per 1000 person-years in the high, moderate, and low IC groups respectively. The incidence of HZ among patients with breast, prostate, lung and bronchus, colon and melanoma cancer was 15, 10, 21, 8, and 9 per 1000 person-years respectively. When compared with the general population, adjusting for age and gender, STM patients in general had ~2-fold increased risk of the general population while patients currently on chemotherapy or corticosteroid therapy had ~3 fold increased risk. Complications of HZ can be a significant burden to the STM patient. The proportion of HZ cases with PHN was estimated to be as frequently as 8% to 42% [13, 35, 36]. Among the HZ cases in STM patients in the KPNC study, it was shown that ~23% had at least one complication (PHN or any non-pain related complications) [13]. PHN (defined as zoster-associated pain persisting or appearing at or beyond 90 days post-HZ onset) occurred in 8.6% of the patients. Multiple dermatome involvement, skin-related, eye related, and neurological complications occurred in 8.5%, 7.7%, 3.2%, and 0.4% of HZ cases respectively.

3.1.2 Rationale for This Study

The epidemiology study conducted by KPNC recently characterized the epidemiology of HZ and its complications in the STM and HM populations. Results of that study confirm that the level of immunocompromise (IC) plays a significant role in the development of HZ and associated complications. Compared to individuals of similar age and sex in the general population, rates of HZ were approximately 5-fold higher in individuals with HM and ~2-fold higher in individuals with STM (~3 fold higher in individuals with STM on chemotherapy or corticosteroid therapy). Among those patients with HM and STM, rates of HZ were higher in individuals with higher levels of IC, than those with low IC levels. The availability of a vaccine to prevent HZ and associated complications in these patient populations represents a significant medical need, as the live attenuated vaccine is contraindicated in immunocompromised individuals.

POC for a VZV vaccine inactivated by heat-treatment for use in HCT recipients was demonstrated in two clinical trials conducted by Arvin, et al. [14, 15]. These trials utilized inactivated Oka/Merck varicella vaccine supplied by Merck & Co., Inc. One of the studies demonstrated reduced morbidity following a 3-dose vaccine regimen, and the other a decreased incidence of disease due to VZV reactivation following a 4-dose vaccine regimen [14, 15]. The results of these two studies demonstrated that inactivated VZV vaccine given to recipients of HCT had significant impact on the development of HZ. Protection appeared to correlate with the reconstitution of T cell immunity against VZV. A 4-dose regimen, with doses given 30 days prior to HCT and 30, 60, and 90 days post-HCT, resulted in a significant reduction in the risk of HZ [15].

The Phase I clinical study of inactivated VZV vaccine, Protocol 002, was conducted by the SPONSOR. Protocol 002 was a randomized, double-blind, multicenter study to evaluate the safety and immunogenicity of VZV vaccine inactivated by heat-treatment in 4 distinct immunocompromised populations: recipients of HCT (allogeneic and autologous), patients infected with HIV with CD4 counts $<200/\text{mm}^3$, patients with HM and patients with STM receiving chemotherapy. The study enrolled 341 adults (50 autologous HCT, 51 allogeneic HCT, 80 HIV-infected, 81 HM, and 79 STM), 18 years of age or older, who were randomized to receive either a 4-dose regimen of V212 inactivated by heat-treatment or placebo. Of the 81 patients with HM, 62 were vaccinated with inactivated VZV vaccine and 19 were vaccinated with placebo; whereas among the 79 patients with STM, 59 received inactivated VZV vaccine and 20 received placebo. The objective of the study was to provide assess the immunogenicity and safety of the inactivated VZV vaccine in a broad group of immunocompromised patients. No safety signals were identified in any of the immunocompromised populations studied. The study demonstrated promising immunogenicity results in the autologous-HCT, STM and HM populations, however less robust responses were seen in the HIV population with low CD4 counts, and responses were poor among those in the allogeneic-HCT study population.

The inactivated VZV vaccine was found to be generally safe and well-tolerated in the POC and Phase I studies, and no differences in the safety profile were observed following 1, 2, 3, or 4 doses of inactivated VZV vaccine in the POC or Phase I studies. The frequencies of injection site adverse experiences, systemic adverse experiences, and SAEs were not higher following subsequent doses for any patient population assessed in Protocol 002.

Overall, the results of the Phase I clinical study, Protocol 002, indicated that the inactivated VZV vaccine is immunogenic and has a favorable safety profile when administered as a 4-dose regimen to adults with HM or STM receiving chemotherapy, which provided a rationale for further development of the inactivated VZV vaccine in the HM and STM populations.

Of important note, formal dose ranging studies are not feasible in HM and STM patients because studies to formally compare the efficacy of different dose regimens would be extremely large and not feasible to conduct in a timely manner. Therefore, this Phase III study has been designed based on the results of the POC and Phase I studies summarized above.

V212-011 is an adaptively designed study which included a planned interim analysis for futility when 50% of the targeted cases of HZ had accrued in each population. The interim analysis was conducted on 29-Oct-2014 for both populations. At this time, clear evidence of futility was demonstrated in the HM arm and on 04-Nov-2014, enrollment and vaccination were stopped in this population. On 19-Nov-2014 close-out procedures were initiated in the HM population. As per the protocol in the event that one population is futile, the other population may continue and contribute to the final analysis. As a result, the use of V212 in patients with STM will be the targeted indication supported by this study, and the objectives have been modified accordingly (Section 2.1). However, additional subjects will not be enrolled in the STM population, and the current sample size will support the final analysis. Thus, the originally planned second interim analysis for futility and efficacy has been canceled because of the risk of a false negative result due to the small number of cases. Furthermore, a final case count of 90 (reduced from the original planned 210) will be targeted in the STM population; this will provide adequate power for the primary endpoint without the need for enrollment of additional subjects.

3.1.2.1 Rationale for Choice of Vaccine Inactivation Method

Inactivation of the VZV vaccine via the heat-treatment targets a reduction of VZV infectious particles to <10 PFU per dose. POC studies of this vaccine in HCT/Bone Marrow Transplant (BMT) recipients demonstrated that this level of residual infectivity content is not required for vaccine efficacy. Inactivation by gamma irradiation further reduces VZV infectious particle content to <0.1 PFU per dose, while preserving antigen level. In Protocol 004, the Phase I study that assessed the safety and immunogenicity of vaccine inactivated by gamma irradiation in healthy 50- to 59-year-old adults, immunogenicity was not affected when the vaccine was inactivated by gamma irradiation doses up to 25 kGy. Therefore, the VZV vaccine to be used for this study and future studies of V212 will be inactivated by gamma irradiation.

3.1.2.2 Rationale for Dose Regimen

This protocol will assess the safety and efficacy of a 4-dose vaccine regimen in patients with STM and HM. Formal dose ranging studies are not feasible in these patient populations because of the large numbers of subjects that would be required to demonstrate statistical differences in immunogenicity or clinical efficacy across study groups receiving different numbers of vaccine doses. Therefore, the decision to assess a 4-dose vaccine regimen in patients with HM, and STM is based upon the considerations presented below.

POC and Phase I Study Results in Autologous HCT Patients

1. The POC studies conducted in patients undergoing HCT evaluated a single-dose post-transplant, a 3-dose regimen post-transplant, as well as a 4-dose regimen, which added a pre-transplant dose [14, 15]. No efficacy was observed in patients who received the single-dose regimen given 30 days post-transplant. The regimen of 3 doses given 30, 60 and 90 days post-transplant resulted in significant decreases in HZ severity but did not impact HZ incidence [14]. The 4-dose regimen with doses given 30 days prior to transplant and 30, 60 and 90 days post-transplant resulted in a significant reduction in the risk of HZ [15].

Phase I Study Results in HM and STM Patients

2. In the Phase I study, Protocol 002, 3 doses of vaccine induced a robust immune response in patients receiving chemotherapy for STM. A small increment in response was shown postdose 4 as indicated measured by IFN- γ ELISPOT or gpELISA [16], which suggests additional benefit of further immunization. A similar kinetics of T cell response was noted in the HM population, even though the overall magnitude of the response was lower in that population. There is a possibility that the increase in immune response following the fourth vaccine dose could confer a true advantage in efficacy (as it does in auto-HCT patients) or duration or protection in STM and HM patients. However, a direct demonstration would require clinical efficacy studies that assess different dose regimens, as was done for the auto-HCT group to establish POC. Such studies are not feasible for the HM and STM populations because of the very large number of patients that would be required.
3. In the Phase I study, Protocol 002, the postdose 4 responses measured by IFN- γ ELISPOT GMC were generally of comparable magnitude in the auto-HCT and STM groups. At postdose 3, responses were higher in the STM group than in the autologous HCT group. However, the postdose 3 response for STM patients was not as high as the postdose 4 response for auto-HCT patients. These findings raise the possibility that, as was demonstrated in the POC studies for autologous HCT, 3 doses of vaccine may not provide sufficient protection in STM patients.

4. The IFN- γ ELISPOT GMC observed postdose 3 and postdose 4 for the HM group was substantial since the fold rise in GMC was comparable to that seen for older subjects in the ZOSTAVAX™ pivotal study. However, it was lower than for either the autologous HCT or STM groups. Therefore, a 3-dose regimen may not provide sufficient protection in HM patients, and a 4-dose regimen may be an appropriate choice in HM patients to further enhance immune responses and establish protective immunity.

Additional Comments

5. An additional consideration is that HM and STM patients undergoing chemotherapy may present varying levels of immunosuppression over time throughout the vaccination period. Thus, if a dose of vaccine is administered at a time of high immunocompromise, this could potentially result in suboptimal responses. Administering multiple doses may help establish more robust and consistent overall immune responses across these populations of patients and result in improved vaccine efficacy.
6. It is not known why a 3-dose regimen of inactivated VZV vaccine does not reduce HZ incidence in auto-HCT patients, while a 4-dose regimen does. This dramatic difference in efficacy between the 2 dose regimens is not reflected in immunogenicity measurements: in the Phase I study, Protocol 002, 3 doses of vaccine induced a robust IFN- γ ELISPOT response in auto-HCT patients while the increase in response postdose 4 was proportionally less. It is possible that the fourth dose of vaccine primarily enhances aspects of the immune response that are critical for efficacy but not captured by the IFN- γ ELISPOT assay. One may speculate that a fourth dose may help with avidity maturation of the T cell response, a relevant consideration since T cell avidity is a major determinant of antiviral immunity. Preliminary animal data support the concept that more immunizations are required for robust avidity maturation than for T cell expansion [40]. Obviously, a formal demonstration in human patients would be too resource intensive to be feasible.
7. Collectively, the above considerations support the use of a 4-dose regimen of the inactivated VZV vaccine in this Phase III efficacy study in the HM and STM populations. Of note, a 4-dose regimen of V212 will also be used in a concurrent Phase III efficacy study in auto-HCT patients.

3.1.2.3 Rationale for Selection of Efficacy Endpoint Measures

This study will use HZ case definitions that are consistent across both the ZOSTAVAX™ and V212 programs. In addition, HZ-associated pain and PHN will be assessed using a validated instrument and procedures common to both programs. Patients with suspected HZ will be evaluated for 6 months to obtain information on the duration and severity of HZ-related pain, the development of HZ complications, and the development of PHN. Pain severity will be measured using the ZBPI, a modified version of the Brief Pain Inventory (BPI) developed by Cleeland et al., to evaluate cancer pain [41]. The ZBPI is specifically designed to measure HZ-related pain and its impact on daily living. The validity and reliability of the ZBPI pain items have been established for HZ through a prospective validation study conducted in 121 patients with HZ [42].

Data for exploratory endpoints, including interference of HZ on ADL, HZ-related HCU, and HZ-related WPQ will be collected, using qualified or validated tools, in order to assess the frequency and magnitude of these HZ outcomes and provide additional confirmation that the vaccine has clinically meaningful impact on HZ disease [41, 42].

3.1.2.4 Rationale for the Immunogenicity Endpoint Measures

An exploratory objective of the study will be to evaluate the immunogenicity of the vaccine in patients with HM and STM. Two candidate immunologic markers of efficacy will be assessed. T-cell-dependent antibody response measured by gpELISA will be assessed only in the STM study group. T-cell response directly measured by VZV IFN- γ ELISPOT will be assessed in a subset of the study population including both the STM and HM study groups.

The gpELISA has been validated and is the primary assay used by the central laboratory for detection of VZV antibodies before and after vaccination with a VZV-containing vaccine. The T-cell dependent antibody response measured by gpELISA was demonstrated to correlate with vaccine efficacy against HZ in two independent large efficacy trials of immunocompetent older adults [43, 44]. The VZV IFN- γ ELISPOT assay has been validated and is used to detect IFN- γ -secreting VZV-specific cells from PBMC before and after vaccination with VZV-containing vaccine(s), thus providing a direct assessment of cell-mediated immunity. Data from ZOSTAVAX™ pivotal efficacy study show that in immunocompetent subjects, immune responses to the vaccine measured by gpELISA and by VZV IFN- γ ELISPOT both correlated with efficacy of the live attenuated zoster vaccine [43].

To assess the gpELISA and IFN- γ ELISPOT results as potential correlates of V212 efficacy in patients with HM and/or STM, serum samples will be collected from all STM patients in the main portion of the study at Day 1/Visit 1 and at Visit 5 and tested via gpELISA. Antibody measurements via gpELISA will not be conducted in patients with HM because the nature of the disease and treatments (e.g., blood products) can bias the results of an antibody assay. A subset (n=1000) of the study population (the first 500 patients with STM and the first 500 patients with HM at participating sites) will participate in a substudy whereby whole blood samples will be collected and tested using the VZV IFN- γ ELISPOT at Day 1/Visit 1 and at Visit 5.

Endpoints for gpELISA include GMT and GMFR from Day 1, and endpoints for IFN- γ ELISPOT include GMC and GMFR. For both assays, the exploratory objective endpoint is the GMFR, since patients are not seronegative at baseline. Also, data from the ZOSTAVAXTM program suggest that baseline values influence postvaccination values.

3.2 STUDY PROCEDURES

Refer to the study flow chart (Section 1.7) for a concise view and timing of the study procedures.

3.2.1 Visit Windows

Each dose of V212 or placebo should be administered every ~30 days. There is a minimum of 20 days of postvaccination follow-up required prior to the subsequent dose of vaccine. The allowable window between each vaccine dose is 20 to 40 days. The minimum follow-up period postvaccination dose 4 is 28 days; the maximum allowable window at Visit 5 is 60 days postvaccination dose 4. Deviations from the permitted visit windows (i.e., the patient meets deferment criteria or the patient is not able to complete the visit as scheduled per protocol because of medical or logistical reasons) require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision on patient management. All study procedures should be performed at the vaccination visits.

3.2.2 Informed Consent

Study personnel must obtain written informed consent from each patient prior to performing any study procedures (e.g., collection of blood sample, vaccination, or rash lesion sample). Consent must be documented by obtaining the dated signatures of both the patient and the person conducting the consent discussion, on the consent form. A copy of the signed and dated consent form will be given to the patient for his/her records.

Should a patient sign a consent form but not enroll in the study on that same day (i.e. no study procedures are performed) that signed consent form would be valid for up to 14 days. If the patient returns after more than 14 days have elapsed, consent procedures must begin again and a new written consent must be obtained.

3.2.3 Assignment of Baseline Number

Baseline numbers will be automatically generated by the SPONSOR via an electronic data management system. Each patient will be assigned a unique baseline number immediately after the informed consent is signed. The baseline number identifies the patient for all study-related procedures that occur prior to receiving an allocation number. Baseline numbers are a combination of the site number and the patient number and are assigned sequentially from the lowest number to the highest number at each site. Baseline numbers should never be skipped and may not be reassigned for any reason. A single study patient cannot be assigned more than 1 baseline number.

3.2.4 Non-Randomized Patients

If a patient has signed a consent form, but the patient is not randomized, the patient's basic demographic information and the reason(s) for exclusion from the study must be reported. The baseline number previously assigned to the patient should be used to uniquely identify this nonrandomized patient. For detailed information on entering data into the data collection system for these patients, consult the electronic data capture (EDC) data entry guidelines provided by the SPONSOR.

3.2.5 Study Participation Patient Identification Card

All subjects/patients will be given a card, at the time of screening, identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

3.2.6 Physical Examination

A physical examination, **including weight**, will be performed at Day 1 by a physician, nurse practitioner, or physician's assistant (in accordance with local law) and will include a general review and evaluation of body systems to determine whether the patient meets enrollment criteria for this study. Physical examination details will be documented in the patient's chart.

3.2.7 Medical History/Conditions

The patient's medical conditions during the 5 years prior to enrollment should be reported, capturing any chronic or serious conditions. In addition, the primary cancer diagnosis, type of malignancy, grade, and stage or classification of disease should also be collected and entered into the database.

3.2.8 History of Varicella-Zoster Virus Infection

To be enrolled in the study, patients must have a prior history of varicella, antibodies to VZV (documented prior to receipt of blood products), or residence in a country with endemic VZV infection. A validated list of countries where VZV is considered endemic does not exist. Operationally, VZV is assumed to be endemic in countries where chickenpox is a typical childhood disease. Patients who reside in regions that have implemented universal varicella vaccination programs will be considered to have resided in endemic regions if they attended school in an endemic region where varicella vaccination had not yet been widely implemented. In areas of the world where it is uncertain if VZV is endemic, study sites are encouraged to perform VZV antibody testing (local laboratory) of potential study participants prior to administration of blood products consistent with standard medical practice. VZV seronegative patients should not be enrolled.

3.2.9 Concomitant Medication(s)/Treatment(s)

Specific prohibited medications/treatments in this study include the following:

- Live virus vaccines at any time beginning 4 weeks prior to dose 1 through 28 days postvaccination dose 4;
- Any varicella or non-study zoster vaccine for the duration of the study;
- Inactivated vaccines beginning 7 days prior to through 7 days following any dose of vaccine or placebo.
 - Thus, inactivated influenza vaccines should not be administered in the time period beginning 7 days prior to through 7 days following any dose of study vaccine or placebo. It is understood that this study will be conducted over multiple influenza seasons. The allowed window for administration of inactivated vaccines should be sufficient to allow for administration of inactivated influenza vaccines. *Of important note, Live influenza vaccine is prohibited at any time beginning 4 weeks prior to dose 1 through 28 days postvaccination dose 4.*
- Receipt of any long term antiviral prophylaxis (duration greater than 4 weeks) with activity against HSV, VZV, or CMV.

All medications, including standard antiviral therapy and pain medications administered for HZ treatment of a HZ case will be permitted as clinically indicated. Other prescription or over-the-counter medications that may be required for pre-existing or concurrent conditions may be used during the study. Chemotherapeutic regimens and/or radiotherapy may be used throughout the study.

It is imperative that all medications administered to the patient 90 days prior to enrollment and any new medications or procedures (e.g. radiation therapy, blood transfusions, chemotherapy, etc.) starting/occurring *through 28 days Postvaccination 4* be recorded.

Medications administered for the treatment of HZ and/or HZ symptom relief, and those medications administered within 14 days of an SAE, and as treatment for an SAE, will be collected for the *duration of the study*.

3.2.10 Contraception

Women who are not of reproductive potential are not required to use contraceptive methods in this study. A female patient who is not of reproductive potential is defined as: one who has either (1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle stimulating hormone [FSH] levels in the postmenopausal range as determined by a laboratory, or 12 months of spontaneous amenorrhea), (2) post-surgical bilateral oophorectomy and/or hysterectomy, or (3) bilateral tubal ligation. Note that the definition surrounding the term "natural menopause" as it relates to 6 or 12 months of amenorrhea is specific to women who are of the expected age of natural menopause and does not pertain to conditions occurring in younger women. Younger women who experience spontaneous amenorrhea are considered to be of childbearing potential.

Women of reproductive potential may be enrolled into the study. However, female patients must agree to remain abstinent or use (or have their partner use) adequate contraception during the time period starting 2 weeks prior to enrollment through 6 months from the last vaccination dose. Acceptable methods of birth control include use of hormonal contraceptives, intrauterine device (IUD), diaphragm combined with spermicidal agent, contraceptive sponge, bilateral tubal ligation, condoms combined with spermicidal agent, or abstinence. Simultaneous use of two reliable forms of contraception is recommended. Females of reproductive potential must have been consistently using these barriers for at least 2 weeks prior to screening to be eligible for randomization.

If there is any question that a patient will not be reliable in the use of the appropriate contraceptive methods, the patient should not be enrolled into the study. Patients must be completely informed of the unknown risk of the vaccine during pregnancy and agree not to become pregnant during the time they enter the study through 6 months from the last vaccination dose.

3.2.11 Pregnancy Testing

A serum or urine pregnancy test (sensitive to 25IU β -hCG) will be performed at the investigative site prior to each vaccination for all female patients of childbearing potential. Pregnancy test results must be available before vaccination. Any patient with a positive pregnancy test must not be vaccinated. Any patient found to be pregnant at the Day 1 visit will not be randomized and will not participate in the study. If pregnancy develops after Visit 1 but before completion of the vaccination regimen, the patient will not receive subsequent vaccine doses but should remain in the study for safety, efficacy and immunogenicity follow-up. The physician will maintain regular contact with the subject for the purpose of pregnancy assessment (term, miscarriage, abortion, etc.). All pregnancies should be reported to one of the study personnel listed on the SPONSOR Contact Information page (located in the Administrative Binder) as soon as the situation becomes known.

NOTE: If required by an institution's IRB/ERC, more frequent pregnancy testing may be performed in accordance with local regulations.

3.2.12 Stratification/Randomization/Allocation

Randomization will be stratified by patient population (STM or HM) with approximately 2696 patients with STM and 2568 patients with HM enrolled into the study. Patients with HM will be further stratified into one of two strata (low IC; moderate to high IC), based on the patient's specific HM diagnosis (underlying cancer diagnosis) and/or chemotherapeutic regimen (see Appendix 6.1). The planned randomization schedule by vaccination group is shown in Section 2.4.2.

An IVRS will be used to register patient visits at the time of randomization and at subsequent visits. The IVRS will be used to allocate the patient to the vaccination group assignment and to assign either V212 or placebo to the patient during randomization, according to a centralized randomization schedule generated by the SPONSOR. Study site personnel accessing the IVRS will be assigned an individual unique personal identification number (PIN). Site personnel must use only their specific assigned PIN to access the IVRS and must not share their assigned PIN with anyone.

A separate allocation schedule will be used to allocate those patients participating in the ELISPOT substudy to assure a well-balanced randomization ratio. All investigative sites participating in the immunogenicity substudy will enroll each consented substudy patient until the target enrollment of 1000 patients has been met.

At Visit 1, after the patient has signed the consent form, the medical history has been collected, all inclusion/exclusion criteria are met, a negative serum or urine pregnancy test (sensitive to 25IU β -hCG) has been obtained, and the prevaccination blood sample has been collected (if applicable), site personnel will access the IVRS using their PIN. The IVRS will assign an allocation number to the patient, followed by the assignment of unique component identification number (CID) corresponding to the vial of vaccine/placebo and diluent the patient should receive at that visit. The CID on the vaccine/placebo vial and the CID on the diluent vial will be unique. The IVRS will automatically assign the appropriate clinical material based on the patient's treatment allocation.

At subsequent vaccination visits (Visits 2, 3, and 4), study personnel will access the IVRS using their PIN and the IVRS will assign a unique CID number corresponding to the vial of V212 or placebo and diluent the patient should receive at that visit. The CID on the V212 or placebo vial and the CID on the diluent vial will be unique from each other as well as previous CID assignments.

The patient's allocation number will remain the number that was assigned to the patient at Visit 1 and will never change.

At the conclusion of each transaction, the IVRS confirms the transaction audibly and provides a detailed confirmation sheet via FAX to the investigator site. This documentation must be retained in the patient's file.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.13 Blood Collection for Immunoassays

Blood will be collected at Visit 1/Day 1 and at Visit 5 (~28 days Postdose 4) in a subset of patients. This study procedure is described in Section 3.3. Blood collection at Day 1 must take place prior to administration of Dose 1 of V212 or placebo.

3.2.14 Vaccination

Approximately 5264 patients (~2632 vaccine recipients; ~2632 placebo recipients), 18 years of age or older (**Note: In India only, enrollment is restricted to patients 18 to 65 years of age.**) will be randomized 1:1 to receive either V212 or placebo given as a 4-dose regimen approximately 30 days apart. Placebo will be the vaccine stabilizer for the V212 with no virus antigen.

3.2.14.1 Dosage and Administration

This is a 4-dose vaccination study. On the day of enrollment, patients will be randomized to the vaccine or placebo group. Each dose of study vaccine or placebo will be administered as a 0.5-mL (*do not administer all of the contents from the vial*) subcutaneous injection preferably in the deltoid region of the arm, alternating arms for each vaccination dose if possible. Each dose should be administered approximately 30 days apart. The minimum window between 2 vaccine doses should be 20 days. All vaccinations should be appropriately recorded in the study data collection system.

3.2.14.2 General Precautions for Administration

Adequate treatment provisions, including epinephrine, should be available for immediate use, should an anaphylactic or anaphylactoid reaction occur.

A separate, sterile syringe and needle or sterile disposable unit should be used for each injection for each patient, to prevent transmission of infectious agents from person to person. Needles should not be recapped and safe disposal procedures for sharps should be followed.

Before subcutaneous injection, the skin over the site to be injected should be cleansed with a suitable antiseptic. After insertion of the needle into the skin, aspirate to ensure the needle has not entered a blood vessel. Should this occur, remove the needle/syringe and discard the needle/syringe and study vaccine or placebo according to local regulations regarding medical/biohazardous waste and note on the Vaccine Accountability Form in the Administrative Binder. Call the IVRS for a replacement vial of study material.

3.2.14.3 Preparation of the Vaccine

Use only the diluent that is provided by the SPONSOR to reconstitute the vaccine. The diluent is sterile distilled water and contains no preservatives or other substances that might adversely affect the vaccine. To reconstitute the vaccine, first withdraw the entire contents of the diluent vial into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine (approximately 0.7 mL) and gently agitate to mix thoroughly. Withdraw and administer 0.5-mL of the reconstituted vaccine.

Do not freeze reconstituted vaccine.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may adversely affect the vaccine. A 5/8-inch (16-mm), 25-gauge needle is recommended for subcutaneous administration of the vaccine/placebo to an average adult.

3.2.14.4 Administration of the Study Vaccine

The study vaccine or placebo should be administered via subcutaneous injection preferably in the upper, outer aspect of the arm (deltoid region), alternating arms for each vaccination dose, if possible.

Details of all vaccinations, including the time the vaccine vial is removed from the refrigerator, administered, site of injection, route of administration, and dose volume should be recorded at the site. Study vaccine or placebo should be administered as soon as possible after reconstitution. If the study vaccine or placebo is not administered within 30 minutes after reconstitution, it should be discarded according to applicable local regulations for medical/biohazardous waste, noted on the vaccine accountability log in the Administrative Binder, and a replacement vial should be obtained. All unused, non-reconstituted study vaccine and diluent should be returned to the SPONSOR upon completion of the study.

3.2.14.5 Replacement Vials

Additional supplies of V212 or placebo will be packaged to account for any unplanned losses. Replacement vials are to be used if an error is made in reconstituting V212 or placebo, if V212 or placebo is not administered within 30 minutes after reconstitution or if a vial of vaccine is accidentally destroyed or improperly handled. Replacement vials for Doses 1 through 4 will be made through IVRS. Refer to the IVRS instruction materials supplied to the study sites.

3.2.15 Clinical follow-up for safety

Please refer to Section 3.4 for safety follow-up information, including VRC data collection and information on adverse event reporting.

3.2.16 Exposure Survey

At Visits 2, 3, 4, and 5, patients will be questioned regarding their exposure to varicella and/or HZ since their last visit. Study personnel will obtain information detailing the patient's exposure to varicella and/or HZ since vaccination. Exposure is defined as contact with an individual from 5 days prior to the onset of a chickenpox rash, or from the day of onset of an HZ rash, until crusting of lesions.

3.2.17 Follow-up of Suspected HZ Cases

3.2.17.1 Definition of a Suspected Case of HZ

Criteria for a suspected HZ case are the development of a papular or vesicular rash with a dermatomal or generalized distribution, or in the absence of a rash, clinical suspicion of VZV infection with or without the detection of VZV in diagnostic specimens from blood, CSF, lung, liver or other organ. In immunocompromised patients, HZ rashes may be atypical, for example involving more than one dermatome, or rash may not be present.

3.2.17.2 Identification of Suspected HZ Cases

Patients will be monitored through the entire study period for clinical signs and symptoms of HZ. Prior to vaccination, study personnel will instruct all patients on the signs and symptoms of HZ.

Typically, acute HZ may include numbness, burning or tingling sensation, and pain at or beneath the skin; maculo-papular lesions along one or more dermatomes which progress to vesicles, followed by crusted lesions. Immunocompromised individuals, however, are at increased risk for developing severe and life-threatening complications as well as severely disabling PHN. For instance, HZ rash may involve 3 or more dermatomes, possibly resulting from hematogenous spread. Also, clinical presentation of HZ may be atypical and non-specific, and include signs and symptoms such as fever, abdominal pain, altered mental status, and respiratory symptoms with or without a rash. Possible serious complications of HZ in immunocompromised individuals include neurological (PHN, cranial neuritis, motor neuropathy, transverse myelitis), ophthalmic (keratitis, iritis, retinitis, visual impairment), and cutaneous (scarring, disfigurement, bacterial superinfection) morbidities. Visceral involvement can also occur which can lead to death due to meningoencephalitis, hepatitis or pneumonitis [45].

Patients will be monitored through the entire study period for clinical signs and symptoms of HZ. Prior to vaccination, all patients will be instructed by study personnel regarding the signs and symptoms of HZ. Patients will be asked to notify study personnel if they experience a rash or other symptoms suggestive of HZ at any time during the study.

All VRCs should be reviewed through 28 days post-dose 4 to identify any varicella/varicella-like or HZ/HZ-like rashes that were not previously examined by study personnel. The patient should be questioned for information on these rashes and the information should be recorded on the appropriate forms.

Monthly contact by telephone, via the internet, or during a follow-up visit will be required for each patient to ascertain complete reporting of suspected HZ.

3.2.17.3 Suspected HZ Case Follow-Up (Cases With HZ and HZ-like Rash)

All patients who experience rash or other symptoms that could be due to a suspected case of HZ should be seen by a medically qualified investigator, (defined as a physician, or in accordance with local regulations, a nurse practitioner or physician assistant) as soon as possible, preferably within 24 to 72 hours of rash onset. The medically qualified investigator's description and assessment of the rash, associated complications and complaints, and the patient's history of exposure to varicella and/or HZ should be recorded on the appropriate eCRFs. In addition, the patient should have a skin lesion swab and blood sample collected for VZV identification by PCR at the initial rash visit. The patient should be evaluated by a medically qualified investigator every 3-5 days until no new skin lesions appear. If the rash is a suspected case of HZ, the patient should undergo all procedures and follow-up visits required for suspected HZ cases.

All patients with suspected cases of HZ will be entered into a 6-month suspected HZ case follow-up. Deviations from the 6-month suspected HZ case follow-up period due to medical or logistical reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision. If a patient has multiple suspected cases of HZ, each case must go through the 6-month follow-up procedures. If a patient with a suspected case of HZ has pain persisting longer than 6 months, he/she should continue in HZ follow-up until the pain resolves or the study ends.

Initial Evaluation of a Suspected Case of HZ With HZ or HZ-like Rash

At the initial evaluation of a suspected case of HZ with HZ or HZ-like rash, the following procedure should be followed:

- a) Perform a full physical examination and report relevant clinical findings. These findings include the dermatome(s) involved, morphologic characteristics of the rash, (including number and type of lesions and extent of rash), and any signs of HZ-associated complications such as disseminated HZ, secondary infections, and hospitalizations and/or mortality related to HZ. At the time of the initial rash assessment, varicella or HZ exposure history should also be obtained. Collect and record all medications administered for HZ treatment or HZ symptom relief.
- b) If rash is present, perform rash assessment to monitor for rash evolution
- c) If skin lesions are present, collect 2 swabs from the skin lesions to send for analysis by PCR as described below. PCR testing is required to confirm the presence of the virus in the lesion as well as to differentiate vaccine-strain from wild-type VZV.

NOTE: If both vesicles and pustules are present, vesicles are the preferred source for specimens. Follow the procedures on lesion sample collection/storage and shipping provided in the Laboratory/Procedures or Administrative Binder.

1) Obtaining the lesion specimen

For vesicular (clear fluid-filled or blister-like) or pustular lesions: Using the scalpel blade, unroof one or more vesicular lesions. Swab and vigorously rub the base of the lesion, absorbing any lesion fluid onto the swab. If lesions are ulcerative, swab and vigorously rub the ulcer base to obtain cellular material. Ensure there is plenty of cellular material and vesicle fluid on/in the swab. Remember to use 1 swab per skin lesion.

NOTE: If both vesicles and pustules are present, vesicles are the preferred source for specimens.

When only macular (i.e. red, flat) and/or papular (raised bump) lesions are present: Use the sterile scalpel blade to unroof one or more lesions. Swab and rub the lesion vigorously enough to ensure that epithelial tissue is obtained. It is more difficult to obtain adequate skin cells from a maculopapular lesion; therefore, this procedure should only be used when there are no vesicular or pustular lesions present.

Scabs or crusted lesions: Using the scalpel, gently lift the scab from the lesion to obtain a piece of the scab and place the scab in the sterile tube. This procedure should only be used when there are no vesicular or pustular lesions present.

NOTE: If the patient develops a suspicious rash after the first evaluation for a suspected case of HZ, the skin lesion specimens should be obtained when the rash is first observed.

- 2) Confirm that the swab contains adequate lesion fluid/cellular material for testing.
- 3) Break off the handle and place the swab in a sterile tube, making sure to securely tighten the screw-top tube. Using the label provided by the SPONSOR, with a fine-point permanent marker include the following information:

Allocation number, baseline number, date, type of specimen (skin lesion) and site (left arm, etc.).

- 4) Repeat steps #1 through #3 for a second skin lesion.
- 5) Place each labeled, screw-top tube into a centrifuge tube. Samples can be stored at -15°C or lower pending shipment.

NOTE: Lesion samples and cold packs should be stored in separate freezers. Skin lesion specimens cannot be stored in a freezer containing a VZV vaccine.

d) Collect blood sample for VZV detection by PCR.

- e) Pain and interference with ADLs will be assessed by completion of the ZBPI by the patient.
- f) HZ-related non-protocol healthcare utilization will be assessed by a study personnel conducted interview with the patient using the HCU questionnaire.
- g) Work and productivity loss will be assessed by a study personnel conducted interview with the patient using the WPQ form.
- h) Functional health status and QoL will be assessed by completion of the EuroQoL questionnaire by the patient.

Visits During Rash Progression

- a) Perform a full physical exam every 3-5 days until no new skin lesions appear. Clinical findings as well as relevant laboratory results must be reported. These findings will include descriptions of the evaluation of dermatomal involvement, and the morphologic characteristics of the rash, including new vesicle formation, number of lesions, and the extent of rash, and any HZ-associated complications. Record all medications administered for HZ treatment or HZ symptom relief.
- b) Repeat steps e through h as above.

Visits Following Cessation of New Lesion Formation

- a) Conduct monthly evaluations for 6 months from HZ rash onset. Assessments may be obtained by telephone or at a study visit. All information should be reported.
- b) Repeat steps e through h as above.

3.2.17.4 Suspected HZ Case Follow-Up (Cases Without HZ/HZ-like Rash)

In immunocompromised patients, the clinical presentation of HZ may not include a rash. In the absence of a rash, suspected cases of HZ will be identified based upon clinical suspicion of VZV infection with or without the detection of VZV in diagnostic specimens from blood, CSF, lung, liver or other organ. Patients will be asked to notify study personnel if they experience other acute symptoms which may be suspicious for HZ, at any time during the study. All patients with suspected acute HZ symptom(s) should be seen by a medically qualified investigator (defined as a physician, or in accordance with local regulations, a nurse practitioner or physician assistant) as soon as possible, preferably within 24 to 72 hours of onset of symptom(s). The medically qualified investigator's description and assessment of the symptoms, associated complications and complaints, and the patient's history of exposure to varicella and/or HZ should be recorded on the appropriate eCRFs. In addition, the patient should have a blood sample collected for VZV identification by PCR at the initial HZ case evaluation visit. The patient should be evaluated by a medically qualified investigator every 3-5 days until no new acute HZ symptoms appear. If a HZ case is suspected, the patients should undergo all procedures and follow-up visits required for suspected HZ cases.

All patients with suspected cases of HZ will be entered into a 6-month suspected HZ case follow-up. Deviations from the 6-month suspected HZ case follow-up period due to medical or logistical reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision. If a patient has multiple suspected cases of HZ, each case must go through the 6-month follow-up procedures. If a patient with a suspected case of HZ has pain persisting longer than 6 months, he/she should continue in HZ follow-up until the pain resolves or the study ends.

Initial Evaluation of a Suspected Case of HZ *Without* HZ and HZ-like Rash

At the initial evaluation of a suspected case of HZ without HZ or HZ-like rash, the following procedure should be followed:

- a) Perform a full physical examination and report relevant clinical findings. These findings include any signs of HZ and HZ-associated complications such as disseminated HZ, visceral or CNS involvement, secondary infections, and hospitalizations and/or mortality related to HZ. At the time of the initial assessment, varicella or HZ exposure history should also be obtained. Collect and record all medications administered for HZ treatment or HZ symptom relief.
- b) Verify that a rash is not present. If rash is present, refer to Section 3.2.17.3.
- c) Collect blood sample for VZV detection by PCR.
- d) Pain and interference with ADLs will be assessed by completion of the ZBPI by the patient.

- e) HZ-related non-protocol healthcare utilization will be assessed by a study personnel conducted interview with the patient using the HCU questionnaire.
- f) Work and productivity loss will be assessed by a study personnel conducted interview with the patient using the WPQ form.
- g) Functional health status and QoL will be assessed by completion of the EuroQoL questionnaire by the patient.

Visits During Acute Phase Progression

- a) Perform a full physical exam every 3-5 days until no new acute HZ symptoms appear. Clinical findings as well as all relevant radiologic and laboratory results must be reported to allow proper adjudication of the case. Local laboratory results of specimens obtained because of clinical need, in the context of standard clinical care may be included in the adjudication package. Record all medications administered for HZ treatment or HZ symptom relief.
- b) Repeat steps d through g as above.

Follow-up Visits

- a) Conduct monthly evaluations for 6 months from HZ rash onset. Assessments may be obtained by telephone or at a study visit. All information should be reported.
- b) Repeat steps d through g as above.

3.2.17.5 Treatment of HZ in Study Patients

Patients who develop suspected HZ should be promptly treated with appropriate antiviral therapy, as well as pain medication and other supportive therapy, as clinically indicated according to the judgment of the treating clinician, guidelines established by the participating institution, and consistent with usual clinical practice. Therapy for HZ, and any HZ- associated pain, or other complications will not be provided as part of the protocol study medications. Any medications administered to the patient should be reported on the appropriate eCRF.

3.2.18 Blinding/Unblinding

This is a double-blind (operating under in-house blinding procedures) study in which the patients enrolled, the investigator(s), and the SPONSOR clinical and laboratory personnel who are directly involved with this study will be blinded to the vaccination group assignment. Additionally, members of the CAC are also blinded to the vaccination group assignment. An unblinded statistician will provide summary data to the DMC, who will be unblinded to vaccination group assignment. The SPONSOR personnel will remain blinded until all patients have completed the study follow-up period, the data have been screened for completeness and accuracy, and any protocol violators have been identified. In addition, all contract laboratory personnel will be blinded to the vaccination group assignment. In order to maintain blinding at the site, the contents of each vial of V212 or placebo, as well as the vial labels, will look identical except for vial specific identifying information (e.g. CID number).

Study personnel should use the IVRS to unblind a patient and to unmask vial identity (vaccine/placebo), if necessary. The SPONSOR will not provide disclosure envelopes with the clinical supplies. Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made to avoid unblinding the patient unless necessary. Prior to unblinding, every effort should be made to contact one of the study personnel listed on the SPONSOR Contact Information page in the Administrative Binder. If unblinding should occur for any reason (either accidental unblinding or emergency unblinding for a SAE), the investigator must promptly document the circumstances on the unblinding log and immediately notify the Merck Clinical Monitor listed on the SPONSOR Contact Information page in the Administrative Binder.

3.2.19 Study Completion Procedures

When the required number of confirmed cases of HZ have accrued, or if the decision is made to terminate the study early following a recommendation made by the DMC based on safety concerns, futile efficacy results from the interim futility analyses, or successful efficacy results from the interim efficacy analysis (see Section 3.5.8.1), the study will begin to enter the close-out phase. If this occurs, the study will continue to allow all patients to complete a minimum of 1 year post-vaccination follow-up for safety and efficacy (including new cases of HZ in these patients). At that time, no additional suspected HZ cases will be accrued, and any patient currently entered into suspected HZ follow-up will complete their 6-month assessment period. All patients must complete at least 1 year of follow-up following the last vaccination prior to completing the study. At the end of the safety follow-up period, all patients will be contacted by telephone to complete the study close-out questionnaire. Data generated from these questions will include any previously unreported symptoms of suspected HZ and SAEs, as well as the patient's final study disposition (e.g., completed, lost to follow-up, death).

3.2.20 Discontinuation/Withdrawal from Study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 3.4 SAFETY MEASUREMENTS - DETAILS.

3.2.20.1 Discontinuation/Withdrawal Criteria

As indicated in Section 2.3.2, a patient who discontinues from the study due to pregnancy or allergic reaction to a component of the vaccine, or who unexpectedly undergoes HCT should not receive subsequent vaccinations but should remain in the study for safety, efficacy and immunogenicity follow-up.

3.2.21 Committees

3.2.21.1 Clinical Adjudication Committee

The CAC is composed of clinical evaluators who are experts in the fields of infectious diseases and oncology, who will adjudicate all suspected cases of HZ as well as any HZ-related complications. Members are external to the SPONSOR, and may include principal or secondary investigators of this study or other V212 studies. No SPONSOR employees are members of the CAC. CAC members are blinded to the study vaccination group assignment. Guidelines that detail the CAC process are described in separate documentation.

3.2.21.2 Scientific Advisory Committee

The Scientific Advisory Committee (SAC), composed of a Merck Clinical Monitor, Merck statistician, Merck Communications Department (MCD) representative and external scientific leaders in the therapeutic area/disease area, convenes to provide advice on the protocol design and statistical analysis plan and to interpret and publish the study results of the clinical trial. The SAC is an advisory collaborative group.

3.2.21.3 Data Monitoring Committee

An independent DMC will be established for continuous safety oversight during the study and to review data at each of the planned interim analyses. To fulfill its responsibilities, the DMC will review safety, tolerability, efficacy and demographic data according to vaccination group assignments periodically during the course of the study (prior to end-of-study unblinding).

The DMC will consist of individuals with pertinent expertise in the field. An unblinded SPONSOR statistician will perform analyses of the unblinded data to be provided to the DMC, but will not be a voting member of the committee. The DMC guidelines and details related to the unblinded statistical analysis of the data will be described in separate documentation.

The board will be responsible for periodically reviewing the available safety data to identify any critical safety issues in adverse experiences or other safety measures in order to make periodic recommendations to the SPONSOR, including recommending whether to terminate the study based on safety concerns. Interim efficacy analyses (details in Section 3.5.8) will also be provided to the DMC for review and recommendations regarding terminating the study early for futility or early success.

The DMC Chairman will be responsible for reporting post-meeting recommendations to a Steering Committee (SC) comprised of Merck Senior Management members who will hold the authority to discontinue the study in the event of overwhelmingly favorable or unfavorable efficacy results or safety concerns.

3.2.21.4 Steering Committee

The Steering Committee (SC), composed of members of Merck Senior Management, will provide the overall scientific direction for the program and will receive and be responsible for deciding upon any recommendations made by the DMC to stop the study early.

3.3 EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY, ETC. MEASUREMENTS

3.3.1 HZ Case Determination

3.3.1.1 Clinical Adjudication

All suspected cases of HZ will go through case adjudication by the CAC in a blinded fashion. The CAC is a committee of adjudicators with expertise in the diagnosis and management of HZ as well as the medical aspects of clinical trials. The CAC will determine if a suspected case is a confirmed case of HZ, in their clinical opinion, and if it is determined that this is a confirmed case; the CAC will make the final determination of the confirmed HZ complication(s) present. Upon case confirmation by the CAC, members will adjudicate the case relative to the composite HZ complication endpoint. For each case of suspected HZ, the study site must obtain all necessary information required for suspected cases of HZ (see Sections 2.5 and 3.2.17). Adjudication packages (AP) consisting of all documents related to the suspected case of HZ will be assembled and distributed to the CAC members for review. Specific details regarding AP contents, endpoint definitions, and adjudication procedures will be found in the V212 HZ Case Adjudication Committee SOP.

3.3.1.2 Final Case Determination

A final confirmed case of HZ is defined primarily on the PCR detection of VZV DNA in a skin lesion specimen. If the skin lesion PCR result is reported as VZV positive, HZ is confirmed. If the skin lesion PCR result is VZV negative, HZ is ruled out. If the skin lesion PCR sample is missing or the result is reported as inadequate, or if the clinical presentation of HZ did not include a rash, the final determination as to whether the suspected HZ case is confirmed is based upon the final CAC adjudication decision in accordance with the CAC SOP.

3.3.2 PCR Assay for Lesion Samples

Lesion samples should be obtained from all patients presenting with a rash associated with varicella or HZ or varicella-like/HZ-like rash at the first evaluation for suspected HZ. If both vesicles and pustules are present, vesicles are the preferred source for specimens. Samples should be collected using the kit supplied by the SPONSOR, and stored immediately at –20°C until shipment. Detailed procedures on lesion sample collection/storage and shipping are provided in the Laboratory Manual.

The purpose of the VZV PCR assay is to detect VZV and herpes simplex virus (HSV) deoxyribonucleic acid (DNA) in specimens obtained from subjects suspected of having varicella or HZ. This is the primary assay used by the central laboratory. The assay is a real-time PCR assay that uses virus-specific primers and probes to detect and discriminate among wild-type/Oka-parent VZV (VZV-WT/VZV-P), Oka-type attenuated VZV (VZV-O), and HSV DNA (HSV types 1 and 2). Virus-specific amplification is multiplexed with β -globin-specific primers and VIC-labeled fluorescent probe to demonstrate the presence of amplifiable host cell DNA in the clinical specimen [46].

The PCR assay is based on TaqMan® sequence detection chemistry utilizing an oligonucleotide probe that is labeled at the 5' end with a fluorescent reporter dye and at the 3' end with a fluorescent quencher dye. This probe sequence lies between 2 amplification primer sequences on the target DNA. When the probe is intact, the proximity of the quencher dye greatly reduces the fluorescence emitted by the reporter dye. If the target sequence is present in the PCR reaction, then the probe anneals between the primer sites and is hydrolyzed by the 5' nuclease activity of TAQ DNA polymerase as this primer is extended. The hydrolysis of the probe separates the reporter dye from the quencher dye, thus increasing the reporter dye signal. As TAQ extends the primer, the probe is removed from the target strand so that the overall PCR process is not inhibited. With each PCR cycle, additional reporter dye molecules are cleaved from their respective probes, resulting in an increase in fluorescence intensity. Each reporter signal is normalized to an internal passive reference dye to adjust for fluorescence fluctuations and baseline corrected. After analysis of the raw fluorescent data by the instrument software, a fixed threshold value of 0.05 is assigned and a threshold cycle (Ct) is determined, which represents the PCR cycle at which reporter fluorescence increased above a baseline signal. The threshold cycle is inversely proportional to the starting concentration of DNA. Results for the assay are reported as the virus type for which the sample is positive: VZVWT, VZV-O, HSV or Negative.

3.3.3 PCR Assay for Whole Blood Samples

All patients presenting with varicella/varicella-like or an HZ/HZ-like rash or acute HZ symptom(s) will have two 10 mL whole blood samples collected in plastic Vacutainer tubes containing EDTA at the first evaluation for suspected HZ. The blood samples should be stored frozen at -20°C until they are shipped to the central laboratory. The DNA isolated from the blood sample will be analyzed by VZV PCR analysis as described in Section 3.3.2. Further details on collection, handling, storage and shipment will be provided in the Administrative or Laboratory Binder.

3.3.4 VZV Antibody gpELISA

Serum samples will be obtained from all patients in the STM study group Day 1 (prior to Dose 1) and at Visit 5 (~28 days Postdose 4) to measure VZV antibody concentrations by gpELISA. Five (5) mL of blood will be collected into a serum separator VACUTAINER tube WITHOUT GEL SEPARATOR. The blood should be allowed to clot in the collection tube for 30 to 60 minutes. Once clotted, the collection tube should not be allowed to sit at room temperature or refrigerated for more than 2 hours prior to centrifugation and separation of the serum from the clot. Do not refrigerate newly collected blood specimens; this will cause hemolysis. Serum should be frozen immediately into approximately 2 to 3 (2-mL) Starstedt tubes, using a sterile pipette, and stored at -20°C until shipment to the central laboratory. The freezer used to store the specimens must be a non-frost-free freezer.

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 the vaccine(s). This method detects antibodies to VZV glycoproteins (gp), which are purified by lectin affinity chromatography from MRC-5 cells infected with the KMcC strain of VZV. 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 purified gp antigens. The assay and the purification of the VZV gp from VZV-infected cells are described [47-49]. Serum sample gpELISA titers correlate with neutralizing antibody titers [50].

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 these 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.

3.3.5 VZV IFN- γ ELISPOT

Approximately 1000 patients from select study sites will be enrolled in the ELISPOT substudy and will have blood samples collected for exploratory purposes to assess for lymphocyte stimulation response to VZV antigen as measured by VZV-specific IFN- γ ELISPOT. The blood samples will be collected for IFN- γ ELISPOT on Day 1 (prior to Dose 1) and at Visit 5 (~28 days Postdose 4). The first 500 patients with STM and the first 500 patients with HM at participating sites will be enrolled into the study. Approximately 60-mL of blood will be collected into tubes containing EDTA or sodium heparin for isolation of PBMCs. Blood samples will be sent to a laboratory qualified in the Merck PBMC procedure for isolation and freezing of PBMCs. The isolated PBMCs will be tested by VZV-specific IFN- γ ELISPOT assay at a central laboratory.

The purpose of the VZV ELISPOT assay is to detect interferon gamma (IFN- γ) secreting VZV-specific cells from PBMCs before and after vaccination with VZV-containing vaccine(s). This assay is performed by IBT Laboratories to evaluate the cellular immune response to the vaccine(s). Results for the assay are expressed as the frequency of spot forming cells (SFCs) per million PBMCs.

The IFN- γ ELISPOT assay utilizes 2 high-affinity IFN- γ specific monoclonal antibodies that are directed against different epitopes on the IFN- γ molecule. In the VZV-specific IFN- γ ELISPOT assay, 5×10^5 PBMCs are stimulated by VZV antigen in wells of cell culture plates that have been precoated with one mouse monoclonal antibody to human IFN- γ . IFN- γ released by the VZV-specific T-cells then binds to the first antibody present in close proximity to the cells that produced it. After ~18 hours in culture, the cells are washed away, and a biotinylated form of the second antibody to IFN- γ is added to the wells of the plate and incubated overnight at 4°C. The plates are washed and then alkaline phosphatase-streptavidin is added to each well of the plate. After 2 hours of incubation at room temperature, the plates are washed again and a chromogenic substrate (NBT/BCIP) is added to react with the alkaline phosphatase. As a result, dark blue spots develop against the white background of the plates. The IFN- γ produced by each cell results in the formation of a spot on the culture plate and the number of spots approximates the number of cells that produced IFN- γ in response to VZV antigen. The frequency of SFCs is usually expressed per million input PBMCs. This reflects the T-cell precursor frequency specific to VZV circulating in the blood at a defined time point. The source of antigen used to stimulate VZV-specific responses is a UV-inactivated virus stock of the Oka/Merck vaccine strain that was produced in MRC-5 cells. A similar preparation from uninfected MRC-5 cells is used as the negative control.

Patients in the ELISPOT substudy will have a separate allocation schedule to assure a well-balanced randomization ratio.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical Measurements for Safety/Vaccination Report Card

3.4.1.1 Safety Follow-up During the Vaccination Period

Each patient will receive a VRC at Visits 1, 2, 3, and 4. On the VRC, patients will be asked to record daily oral temperature measurements on the VRC. Patients should take oral temperature measurements using only the SPONSOR provided standard oral thermometer. Temperature measurements via the otic or axillary methods are not permitted. Patients will also be asked to record on the VRC all adverse experiences during the primary safety follow-up period (postvaccination dose 1 through 28 days postvaccination dose 4), including injection-site adverse experiences and systemic adverse experiences occurring from Day 1 through 28 days postvaccination dose 4. Patients will be asked to record on the VRC any rash at the injection site, as well as any varicella/varicella-like or HZ/HZ-like rashes postvaccination Day 1 through 28 days postvaccination dose 4. Any vaccines other than study vaccines and any medications that are administered during that period should also be documented on the VRC.

The patient will be asked to bring the VRC to the study site at the next scheduled visit. Study personnel will review the VRC for completeness, accuracy, and clarity at each scheduled visit from Visit 2 through Visit 5. All comments are to be reviewed by study personnel and discussed with the patient for clarification, as necessary. Any information gained during VRC review with the patient should be clearly documented, initialed, and dated at the bottom of the VRC. The VRC is considered a source document and no original information recorded by the patient should be crossed out or altered in any manner by study personnel.

All VRC information will be recorded in the Electronic Data Capture (EDC) system. The physician investigator/sub-investigator will determine causality of systemic and injection site adverse experiences recorded on the VRC using the reporting guidelines given in the protocol (Table 3-1) and will classify each event as a SAE (SAE) or nonserious adverse experience (NSAE). If an oral temperature measurement indicates a fever (defined in this study as an oral temperature of $\geq 100.4^{\circ}\text{F}$ or $\geq 38.0^{\circ}\text{C}$), the adverse experience must be reported as such in the database. However, if the fever is a symptom of another reported adverse experience, a separate AE report of fever is not necessary. Refer to the eCRF entry guidelines for details related to AE reporting.

3.4.1.2 Post-Vaccination Safety Follow-up

After the end of the vaccination period (i.e., 28 days postvaccination dose 4), patients will continue to be followed for SAE, regardless of causality, through the end of the study (see Section 3.4.6.1 for additional information on SAEs). Patients will be educated on the criteria for SAE and instructed to call the site immediately if a SAE occurs. In addition, every 3 months (+/- 1 month) beginning 3 months following Visit 5 through the duration of the study, patients will be contacted by study staff either at a scheduled study visit or by telephone, using a pre-specified script, to determine if the patient had a previously unreported clinical adverse experience that met SAE criteria and collect relevant information on SAEs. SAE will be collected as described in Section 3.4.5.1.

In the event the study is terminated sooner than 1 year after the last vaccine dose is administered in this study, the study will continue to allow all patients to complete at least a 1 year post-vaccination safety and efficacy follow-up (including new cases of HZ in these patients).

3.4.1.3 Adverse Experience Toxicity Grading

A vaccine specific toxicity grading scale (Grades 1 through 4) will be applied to all serious and non-serious adverse experiences in this study. During the primary safety follow-up period (through ~28 days postvaccination dose 4), clinical adverse experiences will be recorded on the VRC by the patient at the time of occurrence. The investigator will use the information provided by the patient both on the VRC, and verbally at the time of VRC review, to apply the appropriate toxicity grade (1 through 4). Serious adverse experiences occurring beyond ~28 days postvaccination dose 4 are *not reported* on the VRC. For these events, the investigator will assign the toxicity grade based upon information received at the initial report (and/or subsequent follow-up) of the event. The grade assigned by the investigator will be recorded in the electronic database on the corresponding eCRF. Refer to Appendix 6.2 for Toxicity Grading Tables for injection-site and systemic AEs, respectively.

This adverse experience toxicity grading is in addition to the grading of adverse experiences by maximum intensity (mild, moderate, severe) described in Table 3-1.

3.4.1.4 PCR testing for Miscellaneous Samples in Patients with Serious Adverse Experiences

SAEs suspicious for a VZV infection following the administration of V212 may be associated with the presence of wild-type VZV or with the presence of the Oka vaccine strain. These SAEs may include but are not limited to: pneumonia, pneumonitis, meningitis, cerebritis (encephalitis), cerebellitis (cerebellar ataxia), cerebral vasculopathy, myocarditis, pericarditis, and ocular syndromes (such as retinitis, retinal necrosis and uveitis). At times, it may be important for epidemiological and/or safety purposes to identify the presence of either the circulating wild-type VZV or the Oka vaccine strain of VZV. This identification cannot be made definitively on the basis of clinical presentation or serologic tests. A PCR test has been developed to help distinguish between wild-type and Oka vaccine strain VZV (including differentiation between Oka vaccine strain and wild-type Japanese/Oka strain). This test can be done on live or dead viral specimens. The PCR testing is performed by an independent, academic laboratory at Columbia University, New York, NY.

If a patient develops an SAE suspicious for a VZV infection following the administration of V212, any specimen (e.g., fluid or tissue) that remains following the completion of routine diagnostic testing may be sent to Columbia University College of Physicians and Surgeons, Division of Pediatric Infectious Disease laboratory for VZV PCR testing. This testing is optional for the patient. Written informed consent for PCR testing of these specimens must be obtained. Information regarding the collection, labeling, and shipping of these specimens is provided in the Administrative Binder.

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. 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.

All adverse experiences will be collected from the time the consent form is signed through 28 days following the last vaccine dose (i.e., Dose 4), and such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

Administration of more than one dose of V212 in any 24-hour period, regardless of whether it results in an adverse experience, is considered an overdose for this protocol and must be reported to SPONSOR within 24 hours.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with (“results from”) the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug 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 Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR**3.4.5.1 Serious Adverse Experiences**

Any serious adverse experience, including death due to any cause, which occurs to any subject from the time the consent is signed through the duration of the study, whether or not related to the investigational product, must be reported within 24 hours to the SPONSOR by the electronic data capture system or by paper as outlined in the Administrative Binder.

Additionally, any serious adverse experience 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 one of the individuals listed on the sponsor contact information page (found in the administrative binder) if the event is either:

1. A death which resulted in the subject/patient discontinuing the study
- or
2. A serious adverse experience that is considered by an investigator who is a qualified physician to be possibly, probably, or definitely vaccine related.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-1 for instructions in evaluating adverse experiences.

Table 3-1

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

Maximum Intensity	Mild	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities) Injection site redness or swelling from the day of vaccination through Day 5 post-vacc will be evaluated by maximum size.
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	† Results in death; or	
	† Is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional. Any overdose whether or not associated with an adverse experience must be reported within 24 hours.	
Duration	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
	Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units	
	Did the adverse experience cause the test vaccine to be discontinued?	
	Action taken	
	Relationship to test vaccine	
	Did the test vaccine cause the adverse experience? The determination of the likelihood that the test vaccine caused the adverse experience 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 experience 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 experience (AE):	
	Exposure	Is there evidence that the subject/patient 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?
Relationship to test vaccine (continued)	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
	The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)	
	Dechallenge	(not applicable for vaccines)
Relationship to test vaccine (continued)	Rechallenge	Was the subject/patient reexposed to the test vaccine in this study? If yes, did the AE recur or worsen?

		<p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study.)</p> <p>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/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.</p>
	Consistency with Study 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 scale of 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.		<p>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.</p> <p>Depending on data collection method employed, vaccine relationship may be further graded as follows:</p>
	Definitely related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test vaccine or test vaccine class.
	Probably related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to administration of the test vaccine is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of vaccine relationship		<p>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 there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)</p> <p>Depending on data collection method employed, vaccine relationship may be further graded as follows:</p>
	Probably not related	There is evidence of exposure to the test vaccine. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test vaccine. OR Temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are 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 non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses

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

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

This study is event-driven, with one interim futility analysis and one final efficacy analysis. The interim analysis included futility analyses for individual subgroups (HM and STM). The interim futility analysis was done when at least 50% of the total number of required evaluable HZ cases in each patient population, HM and STM, had accrued. More specifically, the futility analysis was conducted on the HM population when at least 68 cases had accrued in the HM subgroup and the futility analysis was conducted on the STM population when at least 48 cases had accrued in the STM subgroup.

The DMC will monitor safety periodically and will be responsible for reviewing the results of the planned formal interim analyses. The DMC may recommend stopping the study early based on safety concerns or futile efficacy results from the interim futility analysis (see Section 3.5.8.1 and DMC guidelines).

An unblinded SPONSOR statistician who is otherwise unrelated to this protocol will serve as a non-voting member of DMC and will be responsible for performing these preliminary/interim analyses for DMC. Detailed implementation of the interim analysis is described in the DMC charters (separate documentation).

All the interim analysis data will remain blinded to SPONSOR study personnel, the study investigator, the laboratory staff, the CAC members, and the patients throughout the study, until the final database unblinding when all required evaluable HZ cases are accrued.

3.5.2 Hypotheses

Objectives and hypotheses of the study are stated in Section 2.1.

3.5.3 Analysis Endpoints

3.5.3.1 Efficacy

The primary efficacy endpoint is the incidence of confirmed HZ postvaccination in the vaccine and placebo groups in the STM population, defined as the number of HZ cases per 1000 person-years of follow-up (from study enrollment to the end of study). A supportive analysis will consider cases following 4 doses of vaccination based on the time period from the date of Dose 4 to the end of study. Final HZ case determination will be based primarily on the results of the skin lesion PCR. If the skin lesion PCR result is inadequate or missing, or if HZ presentation did not include a rash, case confirmation will be based on the results of case adjudication by the CAC.

Three secondary endpoints are defined for the STM population and in the HM population on an exploratory basis. The three secondary endpoints are defined as follows:

- (1) Each suspected case of HZ will undergo 6 months of follow-up for HZ-associated pain and HZ-associated complications. Moderate to severe HZ-associated pain [defined as 2 or more occurrences of scores 3 or greater (on a 0-to-10 scale)] will be assessed by the ZBPI questionnaire at any time from HZ onset through the end of the 6 month HZ-follow-up period). The response to the question, “Rate your worst pain in the last 24 hours on a 0-to-10 scale” from the ZBPI will be used for the aforementioned HZ pain analyses.
- (2) The HZ-associated complications endpoint is a composite endpoint that is defined as the proportion of patients experiencing at least one of the following HZ complications:
 - Hospitalization or prolongation of hospitalization due to HZ
 - Disseminated HZ (including disseminated HZ rash or VZV viremia)
 - Visceral HZ
 - Ophthalmic HZ
 - Neurologic impairment due to HZ
 - Intravenous acyclovir therapy for HZ

- (3) The incidence of PHN in randomized patients is another secondary endpoint. PHN is defined as pain in the area of the HZ rash with a “worst pain in the last 24 hours” score of 3 or greater (on a 0 to 10 scale) on the ZBPI that persists or appears greater than or equal to 90 days after HZ rash onset. Sensitivity analyses on the comparison of the incidence of PHN persisting or appearing more than 30, 60, 120 and 182 days after HZ rash onset between the vaccination groups will also be performed.

Exploratory efficacy endpoints include:

- The severity-by-duration of HZ pain (defined as the average area under the “worst pain in the last 24 hours” versus time curve) from the first day of HZ onset through 6 months after HZ onset.
- The duration of pain (defined as number of days from rash onset to the first visit when pain score on the ZBPI became persistently < 3).
- The numbers of lesions, number of dermatomes and extent of rash (defined as the maximum area of the HZ rash at each HZ follow-up visit).
- The impact of HZ on ADL, as measured by the score-by-duration of activity-of-daily-interference (ADLI) (defined as the average area under ADLI versus time curve) from the first day of HZ onset through 6 months after HZ onset. ADLI is a single combined score calculated by averaging 7 separate items (regarding general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life) collected in the ZBPI at each HZ follow-up visit.
- The impact of HZ on general health status, as measured by the score-by-duration in the EuroQoL from the first day of HZ onset through 6 months after HZ.
- HZ-related non-protocol-mandated HCU and work and productivity loss. The analyses will be covered in a separate internal SAP, prepared by the Health Economist of the study.

Of note, the exploratory efficacy analyses will be evaluated for the HM and STM populations separately.

3.5.3.2 Immunogenicity

The key immunogenicity endpoints include the GMT and the GMFR from Day 1 (prior to Dose 1), to Visit 5 (28 to 60 days Postdose 4) for the VZV antibody titers as measured by gpELISA in all subjects from STM group. In addition, other endpoints include the percent of patients with ≥ 2 -fold, ≥ 3 -fold and ≥ 4 -fold rises at each time point postvaccination. The same endpoints as for VZV antibody titers measured by gpELISA will be used for GMC as measured by VZV IFN- γ ELISPOT. Using the natural log scale of GMC, the analyses will be performed similarly as for gpELISA to summarize the VZV IFN- γ ELISPOT results collected in the participants in the ELISPOT substudy ($n \sim 1000$) at Day 1 [prior to Dose 1], and Visit 5 [28 to 60 days Postdose 4] for the comparison of GMC between 2 vaccination groups. The exploratory immunogenicity analyses will be evaluated for the HM and STM populations separately.

3.5.3.3 Safety

The minimum safety follow-up period is at least 1 year following the last study vaccination.

The primary safety endpoint of the study will be based on the incidence of SAEs observed during the period up to 28 days Postdose 4 in each vaccination group. Key safety measures for an overall assessment include proportions of patients with (1) any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any SAE, (5) any vaccine-related SAE, and (6) any discontinuation due to an adverse experience. Other key safety parameters include proportions of patients reporting the following adverse experiences:

1. SAEs observed Vaccination Day 1 through 28 days Postdose 4.
2. VRC-prompted systemic adverse experiences (including non-injection site varicella-like rash or HZ-like rash) following any vaccination of V212 or placebo through 28 days Postdose 4.
3. VRC-prompted injection site adverse experiences (such as redness, swelling, and pain/tenderness/soreness) Day 1 to Day 5 following any vaccination of V212 or placebo.
4. Elevated temperature ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$] oral or oral equivalent) following any vaccination of V212 or placebo through 28 days Postdose 4.
5. Any other systemic and injection-site adverse experiences not prompted for on the VRC following any vaccination with V212 or placebo through 28 days Postdose 4.
6. SAEs observed at any time for the duration of the study.

For other adverse experiences not prompted for on VRC, the safety parameters include the incidences of injection-site adverse experiences or systemic adverse experiences after any study vaccination through 28 days Postdose 4 occurring in at least 1% of the patients in either vaccination group.

Incidence of varicella/varicella-like or an HZ/HZ-like rash occurring during the period up to 28 days Postdose 4 will be summarized by skin lesion type (wild type versus vaccine strain) determined by PCR. The rate of SAEs, vaccine-related SAEs and death during the whole period of the study will be summarized per 1000 person-years of follow-up.

The safety analyses will be evaluated for the HM and STM populations separately

3.5.4 Analysis Populations

3.5.4.1 Efficacy Analysis Populations

Modified Intent-To-Treat (MITT) Population

The key summaries and analyses for the primary, secondary and exploratory efficacy endpoints will be based on the MITT population (see Table 3-2). This population will include all randomized patients who received at least one dose of the vaccination. Those randomized patients who are excluded from the MITT population will be listed. The efficacy analyses will be performed based on the treatment group to which those subjects are randomized.

Per Protocol Efficacy (PPE) Population

Supportive analyses for the primary and key secondary endpoints will be conducted in the PPE population (see Table 3-2). This population will include those patients who received all 4 vaccination doses and did not present a case of HZ from Day 1 through 28 days post-dose 4.

To evaluate the risk of PHN or other complications, additional exploratory analyses will also be based on a subset of PPE population that developed HZ.

3.5.4.2 Immunogenicity Analysis Populations

Per Protocol Immunogenicity (PPI) Populations

The immunogenicity summaries and analyses will be provided for the PPI population. To be included in this population, patients must:

- (1) Have received all 4 vaccination doses
- (2) Have not reported any exposure to varicella/HZ within 4 weeks prior to blood draw
- (3) Have not develop any suspected varicella/HZ before the relevant blood sampling
- (4) Have not received medical treatments (such as blood products, immunoglobulin therapy) that may interfere with one or both of the proposed immunogenicity measurements.

Based on criterion (4), some patients may be excluded from only one of the 2 immunogenicity analysis (gpELISA, ELISPOT). The final determination of patients excluded from one or both immunogenicity analyses, and thereby the composition of the Per Protocol immunogenicity analysis populations, will be made prior to the final unblinding of the database and will be documented in a separate memo.

3.5.4.3 Safety Analysis Populations

All patients who receive at least 1 dose of vaccine/placebo and have follow-up data will be included in the safety and tolerability summaries and analyses. The safety analyses will be based on the All Subjects as Treated (ASaT) approach.

3.5.5 Statistical Methods

3.5.5.1 Analysis of Vaccine Efficacy

Table 3-2 summarizes the key efficacy analyses to be performed. The details are given in the following subsections.

Table 3-2

Summary of Key Efficacy Analyses Performed

Analysis	Method	Patient population
Primary		
HZ incidence - VE _{HZ}	Cox proportional hazards regression model with Efron's method of tie handling	MITT
Secondary		
(1) Incidence of moderate to severe HZ-associated pain	Cox proportional hazards regression model with Efron's method of tie handling	MITT
(2) A composite efficacy endpoint of the incidence of HZ complications during the study	Same as above	MITT
(3) Incidence of PHN	Same as above	MITT
Supportive		
HZ incidence - Vaccine efficacy	Cox proportional hazards regression model with Efron's method of tie handling	PP
Durability of efficacy	Kaplan-Meier method Piecewise exponential model	MITT MITT
Exploratory endpoints - Severity-by-duration of HZ pain Duration of pain Score-by-duration of ADLI Score-by-duration of general health status score (EuroQoL) Impact of HCU and Work and Productivity Loss HZ incidence	ANCOVA Summaries ANCOVA ANCOVA Poisson regression with generalized estimating equations Summaries by age categories and HM population	MITT

It should be noted that if a given patient develops two or more episodes of confirmed HZ, only the first episode will be used in the vaccine efficacy analyses. The patients with multiple episodes of HZ will be listed. Exploratory analysis of multiple episodes of HZ (such as the Wei, Lin and Weissfeld method [51]) may also be performed if a sizable proportion (e.g., >10%) of HZ patients develop multiple episodes.

3.5.5.1.1 Analysis of Vaccine Efficacy on Incidence of HZ Cases

The primary efficacy endpoint is the incidence of HZ in the vaccine and placebo groups in the STM population, defined as the number of HZ cases per 1000 person-years of follow-up from study enrollment to the end of study. Vaccine efficacy for HZ (VE_{HZ}) is defined as the relative reduction of the hazard rate of HZ in the V212 group compared with that in the placebo group in STM population. The primary statistical hypothesis for the primary efficacy is $H_0: VE_{HZ} \leq 25\%$ versus $H_1: VE_{HZ} > 25\%$.

To address the primary hypothesis, a Cox proportional hazards regression model in VZV vaccine and placebo recipients stratified by age (< 50 years of age versus ≥ 50 years of age based on a MITT population as described in section 3.5.4.1) will be used as the primary analysis to compare the incidence of HZ between the vaccine and placebo groups. The study time period in the primary analysis will be from the enrollment to the stop date of HZ surveillance. Patients who do not develop HZ will be censored at the stop date of HZ surveillance. The follow-up time for patients who develop HZ will be from the enrollment to their HZ onset date. For the interim analysis, this stop date will be the corresponding database cutoff date for the analysis. Efron's method will be used to handle ties in event times.

A key supportive analysis will include calculation of VE_{HZ} using a PP population as described in section 3.5.4.1 based on Cox proportional hazards regression model. The study time period in the primary analysis will be from the date of Dose 4 to the stop date of HZ surveillance. The model and covariate adjustment will be similar to that noted in the MITT approach. In addition, incidence of HZ and VE_{HZ} will also be summarized by age group (50 to 59, 60 to 69, and 70+) as exploratory analyses.

The results of HZ case determination (PCR versus case adjudication by the CAC) will be summarized by vaccination group. The probability of developing HZ will be estimated and displayed by the Kaplan-Meier method. The incidence rates of HZ post randomization (enrollment) in each group will be compared by the nonparametric log-rank statistic without covariate adjustment. Also, the incidence of HZ will be summarized by vaccination group in terms of number of cases per 1000 person-years in those patients who only received a total of 1 dose, 2 doses, and 3 doses of vaccine/placebo using the MITT population if a sizable proportion (>10%) is observed in each category (1 dose, 2 doses, and 3 doses).

3.5.5.1.2 Analysis of Vaccine Efficacy on Secondary Efficacy Endpoints

Three secondary efficacy endpoints are defined for the STM population and in the HM population on an exploratory basis.

Since the incidences of moderate to severe HZ-associated pain, HZ-complications as defined by the composite endpoint, and PHN are unknown in this population, formal hypothesis testing for these secondary endpoints will not be performed. The incidence of the secondary efficacy endpoints of moderate to severe HZ-associated pain, composite complication endpoint, and the incidence of PHN, defined as pain in the area of the HZ rash with a “worst pain in the last 24 hours” score of 3 or greater (on a 0 to 10 scale) on the ZBPI that persists or appears greater than or equal to 90 days after HZ onset, (point estimate and 95% CI) will be compared between vaccine and placebo groups using Cox proportional hazards regression stratified by age (< 50 years of age versus \geq 50 years of age) based on the MITT population. For patients who develop PHN, the PHN event onset will be the date of HZ rash onset. Patients who do not develop PHN will be considered as censored at the stop date of their HZ surveillance. Furthermore, the count and proportion of each component of the secondary efficacy composite endpoint among all randomized patients in the vaccine and placebo groups will be summarized.

Sensitivity analyses for vaccine efficacy on PHN based on alternative definitions [pain in the area of the HZ rash with a “worst pain in the last 24 hours” score of 3 or greater (on a 0 to 10 scale) on the ZBPI that persists or appears more than 30, 60 120, and 180 days after HZ rash onset] will be compared between the vaccine and placebo groups in the MITT population.

To evaluate the vaccine effect on PHN above and beyond that on HZ incidence, the proportions of patients who develop PHN among HZ cases will be provided by vaccination group. A generalized linear regression model with log-link will be used to estimate the relative risk reduction of PHN among HZ cases in vaccine recipients compared with placebo recipients. This model will include incidence of PHN as a binary response variable, and include vaccination group, and age as covariates. An exploratory analysis will be performed using the similar model, with the use of antiviral drug initiated within 72 hours of HZ rash onset (Yes versus No) added as an additional covariate. Note that these analyses are not protected by randomization, and with the post-randomization variable, antiviral use in the model, the results might be subject to potential bias.

3.5.5.1.3 Analysis of Vaccine Efficacy on Exploratory Endpoints

The following exploratory efficacy analyses will be conducted for the STM and HM populations separately.

To evaluate the vaccine effect on the severity of HZ pain among HZ cases, the severity-by-duration of HZ pain (calculated as the area under the “worst pain in the last 24 hours” versus time curve) will be summarized by vaccination group on a MITT population. To compare the mean severity-by-duration measure of HZ pain among patients who develop HZ between the two vaccination groups, an analysis of covariance (ANCOVA) model adjusting for similar covariates as for the primary efficacy analysis will be used to get the point estimate and a bootstrap method will be used to obtain 95% CI of HZ severity-by-duration scores difference between the vaccination groups. Additional exploratory analysis may include the use of antiviral drug initiated within 72 hours of HZ rash onset (Yes versus No) as an additional covariate.

In addition, the mean and median duration of HZ pain (time from rash onset to the first visit when pain score became persistently < 3) will be provided by vaccination group. The mean HZ pain score, the numbers of lesions, dermatomes and extent of rash (defined as the maximum area of the HZ rash at each HZ follow-up visit), the mean ADLI score and the mean EuroQoL score will be summarized by vaccination group. ANCOVA models will also be used to compare these mean scores between the two vaccination groups at each HZ follow-up visit. In addition, the score-by-duration of ADLI and score-by-duration of general health status score in EuroQoL over 6 months post-HZ onset (calculated by area under the ADLI curve and general health status score curve, respectively) will be summarized by vaccination group and compared by ANCOVA model.

Poisson regression with generalized estimating equations will be used to evaluate the effect of the vaccine on the rates of non-protocol mandated health care utilization and work loss. If the counts of health care contacts in each treatment group are less than 10, then an exact binomial method will be used to calculate the CIs rather than generalized estimating equations.

3.5.5.1.4 Analysis on the Durability of Vaccine Efficacy

To evaluate the durability of vaccine efficacy, the incidence of HZ will be summarized by vaccination group and by every 6 months of follow-up post vaccination. A piecewise exponential model will also be carried out to estimate the vaccine efficacy and the corresponding 95% CI by follow-up interval post vaccination. Note that the estimate may be less precise than the overall estimate, due to smaller numbers of events and follow up in time interval. The durability assessment will be conducted for the HM and STM populations separately.

3.5.5.1.5 Additional Evaluation of Vaccine Efficacy

To further evaluate the vaccine efficacy for HZ, summaries for the incidence of HZ, secondary composite endpoint and PHN in each vaccination group will also be provided by the following subgroups:

- Disease type and HM immunocompromise category (STM, HM low IC or HM moderate to high IC).
- Gender (male versus female)
- Number of vaccine doses received
- Age categories (< 50 years, 50 to 69, and 70+)

3.5.5.2 Analysis of Vaccine Immunogenicity

All immunogenicity analyses are exploratory in this study. The key immunogenicity endpoints include the GMT and the GMFR from prevaccination (Visit 1) at (Day 1 [prior to Dose 1], to Visit 5 [28 to 60 days Postdose 4]) for the VZV antibody titers as measured by gpELISA in all subjects in STM group. A linear mixed longitudinal model will be used on the natural log transformed antibody titers, for the comparison of GMT between 2 vaccination groups across the time points after vaccination. The longitudinal regression analysis model developed by Liang and Zeger [52] will include prevaccination antibody titers and postvaccination antibody titers as response variables. The covariates in the analysis model will include vaccination group, continuous age, visit (indicator for baseline or postvaccination) and vaccination group-by-visit interaction. The antibody titers will be natural-log-transformed in the analyses. The fold-difference between the vaccine and placebo groups and the corresponding 95% CI at the respective visit will be obtained from this model. This analysis will be based on the per-protocol approach. For patients who receive treatments that may interfere with the measurements of VZV-specific antibody response (including those receiving immunoglobulin therapy) or who report an exposure to varicella/HZ within 4 weeks prior to blood draw, or who develop suspected varicella/HZ before the relevant blood sampling, the measurements at corresponding time points and thereafter will be excluded from the gpELISA analysis. The summaries of VZV antibody titers at each time point will also be carried out by vaccine lot at each time point. Patients who receive immunoglobulin therapies will be included in VZV IFN- γ ELISPOT analysis as described below.

To evaluate the association between the immune responses and the risk of HZ, a Cox regression model will be used, which will use the immune responses measured by gpELISA at baseline and at 28 days postvaccination dose 4 as covariates. The GMT and GMFR will also be summarized at these time points by vaccination group and HZ outcome (patients who developed confirmed HZ during the study versus those who did not).

In addition, Cox proportional hazards model will be used to estimate the relation between the occurrence of HZ and the gpELISA titers. The gpELISA titers will be used as the covariate to obtain a risk ratio for HZ per unit increase in the titer.

The percent of patients with ≥ 2 -fold, ≥ 3 -fold and ≥ 4 -fold rises in gpELISA at Visit 5 [28 to 60 days Postdose 4] by vaccination group will also be provided.

The proportion of patients achieving seroresponse ≥ 400 gpELISA units/mL at Visit 5 [28 to 60 days Postdose 4] will be summarized by vaccination group and by HZ status. A supportive analysis may be provided, including all valid immunogenicity results, regardless of protocol deviations. Patients who reported an exposure to varicella/HZ (if any) will be listed and the corresponding count and proportion will be summarized by vaccination group in the tables regarding the exclusion of patients from the per protocol immunogenicity analyses and a brief description of these patients will be provided in the clinical summary section of the Clinical Study Report.

In addition, direct T cell response to VZV antigen as measured by VZV IFN- γ ELISPOT in the ELISPOT substudy participants will be performed at each time point (Day 1 [prior to Dose 1], and Visit 5 [28 to 60 days Postdose 4]). The blood samples will be collected on a subset of ~ 1000 patients. Similar to gpELISA, VZV IFN- γ ELISPOT related summaries and analyses will be considered as exploratory in this study. The same endpoints as for VZV antibody titers measured by gpELISA will be used for GMC as measured by VZV IFN- γ ELISPOT. Using the natural log scale of GMC, the analyses will be performed similarly as for gpELISA for the comparison of GMC between 2 vaccination groups and for the evaluation of the association between the GMC and the risk of HZ.

The key immunogenicity measurements will be summarized at each time point (Day 1 [prior to Dose 1], and Visit 5 [28 to 60 days Postdose 4]) by HZ outcome (patients who developed subsequent confirmed HZ during the study versus those who did not) at each time point. It should be noted that VZV IFN- γ ELISPOT will be performed in a subset of the study population.

3.5.5.3 Analysis of Vaccine Safety

The safety follow-up period will occur for at least 1 year following the last VZV vaccination. Safety and tolerability of V212 will be assessed by evaluation of all relevant safety parameters, focusing on the 28-day follow-up period after any vaccination. The following safety analyses will be evaluated for the HM and STM populations separately.

The primary safety endpoint of the study will be based on the incidence of SAEs observed during the period up to 28 days Postdose 4 in each vaccination group. Two-sided 95% CI on the proportion of any SAE will be provided for each vaccination group based on the exact binomial distribution [19]. To provide an overall assessment, safety measures such as the proportion of patients with (1) any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any SAE, (5) any vaccine-related SAE, and (6) any discontinuation due to an adverse experience will be summarized for both vaccination groups (across any vaccination dosing period and by each vaccination dosing period). The risk differences on these overall safety parameters between the two groups and the corresponding two-sided 95% CI on the risk difference will be provided using the stratified asymptotic methods proposed by Miettinen and Nurminen [20].

To assess the risks of the adverse experiences temporally associated with vaccination, a multi-tiered approach will be used for the analysis of specific safety parameters.

For Tier-1 adverse experiences, risk differences between the two groups, corresponding two-sided 95% CI on the risk difference, and the p-value for the test of significant risk difference will be provided. The corresponding p-value will be based on the normal approximation for testing two independent binomial proportions at the two-sided 0.05 level adjusting for stratification factors. The risk difference and 95% CI will be calculated using the methods proposed by Miettinen and Nurminen [20]. Tier 1 adverse experiences include (1) systemic adverse experiences prompted for on the VRC, including varicella/varicella-like or an HZ/HZ-like rash occurring after any study vaccination through 28 days Postdose 4, (2) injection-site complaints prompted for on the VRC, such as redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 after any vaccination, and (3) elevated temperature ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]), after any study vaccination through 28 days Postdose 4.

Additional summaries on Tier-1 safety parameters will also be provided by the dosing period..

For Tier-2 adverse experiences, risk differences between the two groups and the corresponding two-sided 95% CI on the risk difference will be provided using the methods proposed by Miettinen and Nurminen. This Tier-2 approach will be applied to the proportions of any other injection-site adverse experiences or systemic adverse experiences after any study vaccination through 28 days Postdose 4 that are not prompted for on the VRC but occurred in at least 1% of the patients in either treatment group.

Additional summaries on Tier-2 safety parameters will also be provided by the dosing period, and gender in each vaccination group.

Tier 3 adverse experiences will include summaries for any other adverse experiences after any study vaccination through 28 days Postdose 4.

The rate of SAEs, vaccine-related SAEs and death that occur throughout the entire study follow-up period will also be summarized per 1000 person-years of follow-up by vaccination group, to account for potential differential follow-up time by vaccination group. The probability of mortality will also be estimated and displayed by the Kaplan-Meier curve for each vaccination group. Risk difference and the corresponding 95% CI of these long-term safety parameters between the vaccine group and placebo group will be provided using an asymptotic method for differences of 2 independent Poisson rates. Mortality and SAEs, including vaccine-related SAEs will also be listed by patient with more detailed information.

SAEs and Tier-1 adverse experiences during the primary safety follow-up period will be summarized by body system.

Summaries of varicella/varicella-like or an HZ/HZ-like rash occurring during the primary safety period, through 28 days postvaccination 4, will be provided by vaccination group and by lesion type (wild type versus vaccine strain) determined by PCR. Occurrence of opportunistic infections during the primary safety period (from Day 1 to Day 28 Postdose 4) will also be summarized as adverse experiences. Occurrence of opportunistic infections and recurrence of disease that are SAEs at any time during the study will also be summarized.

3.5.6 Multiplicity

With the decision made from the first interim futility analysis (provided in Sections 1.3 and 1.4), there is only one efficacy analysis performed for the primary efficacy hypothesis in the STM population. As no population enrichment is planned, no multiplicity adjustment will be made for primary efficacy analysis in the STM population and the primary efficacy hypothesis will be tested at one sided $\alpha=0.0125$.

No multiplicity adjustment will be made for the analyses related to the secondary objective and exploratory objectives, including any analyses related to immunogenicity, due to their exploratory nature.

For comparisons of adverse experiences between the vaccine and placebo groups, the goal is to investigate if there exists an overall trend of risk difference between the 2 groups. It is recognized that there exists a multiplicity issue for conducting multiple comparisons on these items, with each comparison being performed at the two-sided 0.05 level (corresponding to the 95% CI). Since the overall significance level for these comparisons will be much >0.05 , caution should be exercised when interpreting the results.

3.5.7 Sample Size and Power

3.5.7.1 Efficacy Analysis

This is an event-driven study. With a 1:1 randomization ratio between the vaccine and placebo groups and a total of 90 HZ cases in the STM population with 2696 patients, the study will have an overall power of ~84.2% to detect 65% VE_{HZ} at the overall two-sided 0.025 significance level, based on the success criterion of the lower bound 97.5% CI for VE_{HZ} being greater than 25%. Table 3-3 also provides power for a variety of assumed vaccine efficacy.

Table 3- 3 Power for Primary Efficacy in the STM Population with 90 Cases

Cases	Power at assumed vaccine efficacy (VE)					
	VE=80	VE=75	VE=70	VE=65	VE=60	VE=55
90	99.9%	99.2%	95.0%	84.2%	66.6%	46.7%

To accrue ~90 confirmed HZ cases in the STM population during the time period from enrollment through approximately the end of maximum 5 years postvaccination, enrollment of approximately 2696 patients (1348 receiving vaccine and 1348 receiving placebo) will be required, assuming 1) 30% total lost-to-follow-up, 2) an HZ rate of 17 per 1000 in the placebo group, 3) VE_{HZ} =65%, and 4) 36 months of study enrollment. The sample size calculation follows the methods described in Lachin [21].

The dropout rates and the HZ event rates will be monitored on an ongoing basis using the blinded database. If the observed HZ case accrual rate indicates that more than 5 years of patient follow-up will be necessary to accrue the targeted number of confirmed cases, then the SPONSOR will consider it beyond the adjustment cap and terminate the study without extended follow-up time and increasing enrollment. Because of the event driven design, no additional interim analysis is expected to be performed when follow-up time is extended or when enrollment is increased. Should enrollment increase, patients enrolled under this scenario will also be followed for safety and efficacy for at least 1 year following receipt of their last dose of V212 or placebo.

Since the incidence of clinically significant pain, complications as defined by the composite secondary endpoint and PHN are unknown in this population, formal hypothesis testing for these secondary endpoints will not be performed, but rather the analysis will focus on the estimation of the vaccine efficacy on these endpoints. To quantify the precision of the analysis, as an example, if the underlying true vaccine efficacy for any one of these secondary endpoints is 52%, and 10% of HZ cases developed a secondary endpoint for vaccine and placebo group, then at interim and final analysis where the HZ case split between vaccine and placebo has met the statistical success criterion for the primary hypothesis, the point estimates and CIs (adjusting for multiplicity) on the secondary endpoints efficacy are roughly 50% (- 80%, 88%) and 40% (-50%, 77%), respectively. If 20% of HZ cases developed a secondary endpoint, then the above point estimates and CIs are 48% (-24%, 80%) and 44% (-1%, 71%), respectively. If 40% of HZ cases developed a secondary endpoint, then the above point estimates and CIs are 48% (5%, 72%) and 43% (11%, 64%), respectively.

3.5.7.2 Safety Analysis

If no SAEs are observed in 1348 STM patients who received V212, this study provides 97.5% confidence that the true SAE rate is <0.28% (1 out of every 362 patients).

The probability of observing at least one SAE in this study depends on the number of patients enrolled and the incidence rate of SAEs in the general population. If the incidence rate of a SAE is 1 of every 838 recipients of the vaccine (0.12%), then there is an 80% chance of observing at least one such SAE among 1348 patients in the vaccine group. If the incidence rate is 1 of every 1943 recipients (0.05%), there is a 50% chance of observing at least one SAE.

For safety comparisons, risk differences between the 2 vaccination groups that could be detected with a 80% probability are summarized in Table 3-4 for a variety of hypothetical true incidence rates. These calculations assume there are 1348 and 1348 STM patients for safety in the vaccine and placebo groups and are based on a 2-sided significance level of $\alpha = 0.05$. No multiplicity adjustments were made in these calculations.

Table 3-4
Differences in Incidence of Adverse Experience Rates Between the Two
Vaccination Groups That Can Be Detected With an ~80% Probability and a Two-Sided
Significance Level of 0.05, With Total 2696 STM Patients

True Incidence Rate of Adverse Experience in Vaccine Group (%)	True Incidence Rate of Adverse Experience in Placebo Group (%)	Detectable Percentage Points Difference in Incidence Rates of Adverse Experiences
0.5	1.59	1.09
1	2.39	1.39
3	5.12	2.12
5	7.61	2.61
8	11.16	3.16
10	13.45	3.45
20	24.46	4.46
30	35.03	5.03
Note: These incidence rates are hypothetical and do not represent actual incidence rates of specific adverse experiences in either group.		

3.5.7.3 Immunogenicity Analysis

All immunogenicity analyses in this study are exploratory. A subset of patients (n ~ 1000) will participate in the ELISPOT substudy and undergo testing for direct VZV T-cell responses by IFN- γ ELISPOT assay. This substudy size is required to adequately power ($\approx 70\%$) the study to detect correlation with efficacy for combined STM and HM population when assuming the true correlation is one unit increase of log scaled post dose 4 ELISPOT GMC will reduce the HZ risk by 18% and standard deviation of log scaled post dose 4 ELISPOT GMC is 2.2 for HM and 1.6 for STM. This substudy size also provides sufficient power ($>88\%$) for each subgroup population for testing fold difference at lower bound of 1.0 when the true fold difference between two groups is 2.0.

In addition, T-cell responses will be indirectly measured using an antibody measure, gpELISA in all patients from STM subgroup. The GMT or GMC and GMFR for gpELISA and ELISPOT will be provided by vaccination group at scheduled time points (see Section 1.7). A longitudinal regression model will be used to estimate the fold difference at these time points between the vaccination groups, while adjusting for the prevaccination titers. Other exploratory analyses will also be performed to determine whether these VZV-specific immune responses are associated with protection against HZ using Cox proportional hazards models.

3.5.8 Interim Analysis

There was one interim futility analysis for individual subgroups (HM and STM). The purpose of the interim futility analysis was to terminate the study if vaccine efficacy was lower than expected in either population or to terminate the combined study if vaccine efficacy was lower than expected in both populations. See Appendix 6.3 for a summary of the interim analysis strategy.

3.5.8.1 Interim Analyses of Futility/ Efficacy for Potential Early Study Termination

The first interim analysis for futility was conducted on 29-Oct-2014. Text describing the analysis strategy can be found in Appendix 6.3.

3.5.8.2 Interim Monitoring of Safety by Data Monitoring Committee

The DMC will monitor safety closely during the study enrollment period in order to ensure the safety of the participants. In the event that SAEs, vaccine related death, or incidence of HZ are noted to be excessive in the vaccine group relative to the placebo group, the DMC may consider stopping recruitment into the study. In the planned formal interim analyses, the SAEs, Tier-1 and Tier-2 vaccine safety parameters will be summarized and analyzed according to the plan specified in Section 3.5.5.3.

An unblinded SPONSOR statistician who is otherwise unrelated to this protocol will serve as a non-voting member of DMC and will be responsible for performing the interim analyses for DMC. Detailed implementation of the interim analyses is described in the DMC guidelines (separate documentation).

3.5.8.3 Interim Monitoring Guidelines for the Data Monitoring Committee

Interim Monitoring Guidelines for the DMC have been developed to describe in detail the membership, organization, functions and responsibilities of the DMC. These guidelines also include the detailed implementation plan of the interim monitoring of efficacy and safety as described in the previous subsections. The DMC guidelines will be described in a separate document.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Product Description

Investigational materials will be provided by the SPONSOR as summarized in Table 3-5.

Table 3-5
Product Descriptions

Product Name & Target Potency	Dosage Form	Comments
PCI [REDACTED]	Single 0.5mL Dose Lyophilized Powder for Subcutaneous Injection	Store refrigerated at 2°C to 8°C or colder. Protect from light.
Placebo	Single 0.5mL Dose Lyophilized Powder for Subcutaneous Injection	Store refrigerated at 2°C to 8°C or colder. Protect from light.
Sterile Diluent for reconstitution of vaccines (sterile water)	0.7mL (fill volume) Sterile solution for reconstitution	Store at room temperature 20°-25°C or refrigerated at 2°C to 8°C.
V212 [†] = Inactivated Varicella Zoster Virus Vaccine		

3.6.2 Packaging Information

Blinded, single-dose vials will be supplied to the clinical sites. Supplies will be affixed with a clinical label in accordance with regulatory requirements.

3.6.3 Clinical Supplies Disclosure

The IVRS should be used in order to unblind patients and to unmask drug identity. The SPONSOR will not provide disclosure envelopes with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the investigator will attempt to contact the Clinical Monitor or Clinical Research Associate. Any unblinding that occurs at the site must be documented.

If unblinding should occur for any reason (either accidental unblinding or emergency unblinding for a SAE), the investigator must promptly document the circumstance on the unblinding log and immediately notify the Merck Clinical Monitor listed on the SPONSOR Contact Information page in the Administrative binder.

3.6.4 Storage and Handling Requirements

Please see Product Description Table (Table 3-5).

Store V212/placebo, and sterile diluent according to their respective product labels.

V212/placebo and sterile diluent supplies will be shipped to the sites at room temperature **or refrigerated, and will contain a** temperature monitoring device. Upon receipt at the investigational site, supplies should be removed from the outer secondary shipping box.

V212/placebo must be placed immediately into the refrigerator. The temperature monitoring device must be de-activated upon receipt of the shipment. Directions for de-activation are specified in the Temp Tale Form (*Instructions to Site*), which are enclosed with each shipment. The temperature monitoring device will indicate whether the shipment has remained within the specified temperature range during transit. If a temperature excursion is indicated, immediately store the product according to the labeled storage conditions (until instructed otherwise), confirm the shipment in the IVRS, and immediately notify the SPONSOR (Clinical Research Associate [CRA]). Return the temperature monitoring device according to instructions accompanying the shipment.

Sterile diluent for reconstitution of vaccines may be stored at room temperature *20 to 25°C (68 to 77°)* or at *2°C to 8°C (35.6°F to 46.4°F)*.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained. Supplies should be stored in the original nested box with the lid closed to minimize exposure to light.

For V212/placebo, if the refrigerator rises above 8°C, study vaccinations should be suspended, the excursion must be registered in the IVRS and the SPONSOR (CRA) should be contacted immediately.

For sterile diluent (if storing refrigerated), if the refrigerator deviates from the 2°C to 8°C (35.6°F to 46.4°F) range, study vaccinations should be suspended, the excursion must be immediately registered in the IVRS and the SPONSOR (CRA) should be contacted immediately.

Vaccine and sterile diluent must NOT be frozen.

It is strongly recommended that a non-frost free laboratory grade refrigerator is used to store the study vaccine. This type of refrigerator is less likely to have wide temperature fluctuations, so it will be more likely to stay within the 2°C to 8°C (35.6°F to 46.4°F) temperature range. A daily refrigerator temperature log must be maintained at the site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder. The temperature log will be reviewed by the CRA throughout the study. An appropriate back up system (i.e. alarm, generator) and study site personnel telephone numbers should be in place in the event of a refrigerator failure.

3.6.5 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the study. The CRA should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical supplies must be returned as indicated in the Sponsor Contact Information. Partial or empty vaccine vials should be properly discarded as biohazardous waste. U.S. sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative for review of shipment and form before shipping. Sites outside of the United States should check with local country Merck personnel for appropriate documentation that needs to be completed for vaccine accountability.

3.6.6 Distributing to Sites and Dispensing to Patients

Study personnel will have access to an IVRS to allocate patients, to assign vaccine to patients 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

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens (VZV Identification) for this protocol will be provided by the SPONSOR as follows:

- Lesion specimens and whole blood specimens for varicella zoster virus (VZV) identification by polymerase chain reaction (PCR) assay which are required to be collected as per protocol (Sections 3.3.2 & 3.3.3). Procedures for the collection, storage and shipping of these samples are available in the Laboratory Binder provided by the Central Laboratory.
- If a patient develops an SAE suspicious for a varicella zoster infection following the administration of V212, optional testing of any specimen (e.g., fluid or tissue) that remains following the completion of routine diagnostic testing may be sent (with the permission of the patient) to Columbia University College of Physicians and Surgeons, Division of Pediatric Infectious Disease laboratory for PCR testing to determine if VZV is present, and if so, which strain (Oka or wild-type, including differentiation between Oka vaccine strain and wild-type Japanese/Oka strain) is present (Section 3.4.1.4). Information regarding the collection, labeling and shipping of these specimens is provided in the Administrative Binder, provided by the SPONSOR. A separate informed consent, provided by the SPONSOR must be obtained for these specimens.

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

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

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

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

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

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

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. 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 study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) 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.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

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

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

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written 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 study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, <http://clinicaltrials.gov/>. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study 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 study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), 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.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single 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 should meet conditions 1, 2, and 3. Significant contributions to study 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 study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend 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 study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

5. LIST OF REFERENCES

1. Schmader K. (2007) Herpes zoster and postherpetic neuralgia in older adults. *Clin Geriatr Med* 23, 615-632.
2. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. *Acquir Immune Defic Syndr*. 2005; 40(2): 169-174.
3. Mattiuzzi GN, Cortes MT, Reuben J, Rios MB, Shan J, et al. Development of varicella-zoster infection in patients with chronic myelogenous leukemia treated with imatinib mesylate. *Clin Cancer Res*. 2003; 9:976-80.
4. Wung PK, Holbrook JT, Hoffman GS, Tibbs AK, Specks U, Min Y, et al. Herpes zoster in immunocompromised patients: incidence, timing, and risk factors. *Am J Med*. 2005;118 (12):1416e9-1416e18.
5. Gourishankar S., McDermid J.C., Jhangri G.S., & Preiksaitis J.K. (2004) Herpes zoster infection following solid organ transplantation: Incidence, risk factors and outcomes in the current immunosuppressive era. *Am J Transplant* 4, 108-115.
6. Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. *Clin Infect Dis*. 2003; 36: 877-82.
7. Ragozzino M.W., Melton L.J., III, Kurland L.T., Chu C.P., & Perry H.O. (1982) Population-based study of herpes zoster and its sequelae. *Medicine (Baltimore)* 61, 310-316.
8. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc Royal Soc Med*. 1965; 58: 9-20.
9. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med*. 1995; 155: 1605-9.
10. Dworkin R.H., Corbin A.E., Young J.P., Jr., Sharma U., LaMoreaux L., Bockbrader H., Garofalo E.A., & Poole R.M. (2003) Pregabalin for the treatment of postherpetic neuralgia. A randomized, placebo-controlled trial. *Neurology* 60, 1274-1283.
11. Tauro S., Toh V., Osman H., & Mahendra P. (2000) Varicella zoster meningoencephalitis following treatment for dermatomal zoster in an alloBMT patient. *Bone Marrow Transplant* 26, 795-796.
12. Walton R.C. & Reed K.L. (1999) Herpes zoster ophthalmicus following bone marrow transplantation in children. *Bone Marrow Transplant* 23, 1317-1320.

13. Habel L.A., Ray G.T., Horberg M., Yawn,B.,Li Y. et al. Herpes zoster in solid tumor and hematologic malignancy patients - A cohort study in a managed care organization [poster]. Presented at the 34th Annual Meeting of the European Society of Medical Oncology;2009 Sep 20-24; Berlin, Germany; ESMO;2009. Poster.
14. Redman R.L., Nader S., Zerboni L., Liu C., Wong R.M., Brown B.W., & Arvin A.M. (1997) Early reconstitution of immunity and decreased severity of herpes zoster in bone marrow transplant recipients immunized with inactivated varicella vaccine. *Journal of Infectious Diseases* 176, 578-585.
15. Hata A., Asanuma H., Rinki M., Sharp M., Wong R.M., Blume K., & Arvin A.M. (2002) Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. *New England Journal of Medicine* 347, 26-34.
16. MRL Data on File, Multicenter study trial of safety and immunogenicity of inactivated varicella zoster vaccine in immunocompromised patients (Protocol 002).
17. MRL Data on File, Multicenter study trial of safety and immunogenicity of inactivated varicella zoster vaccine in healthy adults (Protocol 004)
18. StatXact 7 PROCs for SAS Users Manual 2005; 241-254.
19. Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika* 1934; 26:404-13.
20. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985;4:213-26.
21. Lachin JM. Biostatistical methods: the assessment of relative risks. 2000; 409-412.
22. Goffinet D.R., Glatstein E., & Kaplan H.S. (1973) Herpes zoster infections in lymphoma patients. *Natl Cancer Inst Monogr* 36, 464.
23. Guinee V.F., Guido J.J., Pfalzgraf K.A., Giacco G.G., Lagarde C., Durand M., Van Der Velden J.W., Löwenberg B., Jereb B., Bretsky S., Meilof J., Hamersma E.A.M., Dische S., & Anderson P. (1985) The incidence of herpes zoster in patients with Hodgkin's disease. *Cancer* 56, 642-648.
24. Gopal R., Advani S.H., Dinshaw K.T., Nair C.N., & Desai P.B. (1980) Herpes-zoster in malignancy. *J Assoc Physicians India* 28, 125-132.
25. Pahuja R., Parikh P.M., Charak B.S., Rawat R.S., Gopal R., Saikia T.K., & Advani S.H. (1988) Zoster-varicella infection in Hodgkin's disease. *J Assoc Physicians India* 36, 321-322.

26. Rusthoven J.J., Ahlgren P., Elhakim T., Pinfold P., Reid J., Stewart L., & Feld R. (1988) Varicella-zoster infection in adult cancer patients. A population study. *Archives of Internal Medicine* 148, 1561-1566.
27. Morison W.L. (1974) Herpes simplex and herpes zoster in neoplasia [letter]. *Lancet* 1, 1293.
28. Maung Z.T., Taylor P.R.A., Robinson P., Moore J., Lucraft H.H., Evans R.G.B., & Proctor S.J. (1993) Patient education for self-referral and on-demand treatment for herpes zoster in lymphoma patients. *Leuk Lymphoma* 11, 447-452.
29. Kim S.J., Kim K., Kim B.S., Lee H.-J., Kim H., Lee N.-R., Nam S.-H., Kwon J.H., Kim H.J., Sohn S.K., Won J.-H., Lee J.H., Suh C., Yoon S.-S., Kim H.J., Kim I., Do Y.-R., Lee W.-S., Joo Y.-D., Shin H.J., & Korean Multiple Myeloma Working Party (2008) Bortezomib and the increased incidence of herpes zoster in patients with multiple myeloma. *Clin Lymphoma Myeloma* 8, 237-240.
30. Chanan-Khan A., Sonneveld P., Schuster M.W., Stadtmauer E.A., Facon T., Harousseau J.-L., & Ben-Yehuda D. (2008) Analysis of Herpes Zoster Events Among Bortezomib-Treated Patients in the Phase III APEX Study. *J Clin Oncol* 26, 4784-4790.
31. Tran T.N., Ray G.T., Saddier, P, Trigg, M & Hayes, N. Immunocompromised status of patients with hematologic and solid tumor malignancies: construction of a practical algorithm[abstract]. In: *Proceedings of the 51st Annual Meeting of the American Society of Hematology*;2009 Dec 5-8; New Orleans, Louisiana (LA); ASH;2009. p 980. Abstract nr 2484.
32. Hughes B.A., Kimmel D.W., & Aksamit A.J. (1993) Herpes zoster-associated meningoencephalitis in patients with systemic cancer. *Mayo Clin Proc* 68, 652-655.
33. Feld R. & Bodey G.P. (1977) Infections in patients with malignant lymphoma treated with combination chemotherapy. *Cancer* 39, 1018-1025.
34. Eilers Jr. R.E., Gandhi M., Patel J.D., Mulcahy M.F., Agulnik M., Hensing T., & Lacouture M.E. (2010) Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. *JNCI Cancer Spectrum* 102, 47-53.
35. Dunst J., Steil B., Furch S., Fach A., Bormann G., & Marsch W. (2000) Herpes zoster in breast cancer patients after radiotherapy. *Strahlenther Onkol* 176, 513-516.
36. Huberman M., Fossieck B.E.J., Bunn P.A.J., Cohen M.H., Ihde D.C., & Minna J.D. (1980) Herpes zoster and small cell bronchogenic carcinoma. *Am J Med* 68, 214-218.

37. Feld R., Evans W.K., & DeBoer G. (1980) Herpes zoster in patients with small-cell carcinoma of the lung receiving combined modality treatment. *Ann Intern Med* 93, 282-283.
38. Masci G., Magagnoli M., Gullo G., Morengi E., Garassino I., Simonelli M., & Santoro A. (2006) Herpes infections in breast cancer patients treated with adjuvant chemotherapy. *Oncology* 71, 164-167.
39. Feld R., Evans W.K., & DeBoer G. (1982) Herpes zoster in patients with carcinoma of the lung. *Am J Med* 73, 795-801.
40. Turner MJ et al. Avidity maturation of CD8+ memory T cells is limited by self-antigen expression. *J Exp Med* 205(8) 1859-1868
41. Cleeland CS. et al. Assessment of Pain in Cancer: Measurements Issues. *Advances in Pain Research and Therapy* 1990; 16: 47-55.
42. Coplan PM. et al. Development of a Measure of the Burden of Pain Due to Herpes Zoster and Postherpetic Neuralgia for Prevention Trials: Adaptation of the Brief Pain Inventory. *The Journal of Pain* 2004; 5(6): 344-356.
43. MRL Clinical Study Report, Multicenter Study: Trial of varicella-zoster vaccine for the prevention of herpes zoster and its complications (Protocol 004).
44. Oxman MN. A Vaccine to Prevent Herpes Zoster and Postherpetic neuralgia in Older Adults. *NEJM* 2005; 22:2271-2284.
45. Dworkin RD et al. Recommendations for the management of herpes zoster. *CID* 2007;44 (Suppl 1) SI-26
46. Harbecke R, Oxman MN, Arnold BA, Ip C, Johnson GR, Levin MJ, et al. A Real-Time PCR Assay to Identify and Discriminate Among Wild-Type and Vaccine Strains of Varicella-Zoster Virus and Herpes Simplex Virus in Clinical Specimens, and Comparison With the Clinical Diagnoses. *J Med Virol* 2009;81:1310-22.
47. Keller PM, Lonergan K, Neff BJ, Morton DA, Ellis RW. Purification of individual varicella-zoster virus (VZV) glycoproteins gP, gP_{II}, and gP_{III} and their use in ELISA for detection of VZV glycoprotein-specific antibodies. *J Virol Methods* 1986;14(2):177-88.
48. Wasmuth EH, Miller WJ. Sensitive enzyme-linked immunosorbent assay for antibody to varicella-zoster virus using purified VZV glycoprotein antigen. *J Med Virol* 1990;32(3):189-93.
49. Provost PJ, Krah DL, Kuter BJ, Morton DH, Schofield TJ, Wasmuth EH, et al. Antibody assays suitable for assessing immune responses to live varicella vaccine. *Vaccine* 1991;9(2):111-6.

50. Krah DL, Cho I, Schofield T, Ellis RW. Comparison of gpELISA and neutralizing antibody responses to Oka/Merck live varicella vaccine (Varivax®) in children and adults. *Vaccine* 1997;15(1):61-4.
51. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 1989;84(408):1065-73.
52. Liang K. and Zeger S. Longitudinal data analysis of continuous and discrete response for pre-post designs. *Sankhya* 2000; 62:134-8.
53. Hwang IK, Shih WJ and Decani JS. Group sequential designs using a family of type I error probability spending functions. *Statistics in medicine* 1990; 1439-1445.
54. East Version 4 User Manual 2005; 897-899.
55. Jennison C and Turnbull BW. Group Sequential Methods with Application to Clinical Trials. 2000; 171-181.

6. APPENDICES

6.1 IMMUNOSUPPRESSION CATEGORIES: HEMATOLOGIC MALIGNANCY

The following information provides guidance on the determination of Immunosuppression Category in individuals diagnosed with a hematologic malignancy. The list of treatment regimens is not intended to be an all-inclusive list as it is recognized that treatment regimens will change over the course of the study. Among individuals diagnosed with hematologic malignancy, both the specific HM diagnosis and treatment regimen cause immunosuppression. The impact of the disease and stage of the disease on immune status depends largely on the specific HM diagnosis, as does the treatment prescribed. Table 6-1 presents the decision criteria for determination of the Immunocompromised Category used for stratification of study participants.

Table 6-1

Decision Criteria for Immunosuppression Category

The specific HM diagnosis and/or disease stage is classified as moderate or high for potential to cause immunosuppression (see Table 6-2) OR Treatment regimen includes agents listed in the moderate, high/very high class up to and including 6 months post-cessation of treatment (see Table 6-3 and Table 6-4)	Moderate to High Immunosuppression
None of the above conditions have been met	Low Immunosuppression

The following information and accompanying tables provide support for decision making related to the determination of the Immunosuppression Category. Table 6-2 provides a list of diagnoses within the HM group and the expected level of immunosuppression related to that disease entity.

Table 6-2

Levels of Immunosuppression by HM and Stage

HM Diagnosis	Level of Immunosuppression
Acute leukemia and high grade lymphoma (i.e. Burkitt's lymphoma or T cell lymphoblastic lymphoma)	High
All HM diagnoses not listed as high or low level of immunosuppression in this table	Moderate
Chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), low grade lymphoma including small lymphocytic lymphoma (SLL) Low stage CLL, follicular lymphoma (Stage 0 or 1), Hodgkin's disease (HD) (Stage 1), multiple myeloma, and MDS International Prognostic Scoring System 0-1 (IPSS)*	Low
*For low stage CLL, follicular lymphoma, Hodgkin's disease and multiple myeloma, stage/grade of disease (if available) may be important in determining level of immunosuppression. For patients with MDS, an IPSS score of greater than 0-1 may indicate moderate or high level of immunosuppression depending upon degree of cytopenia, number of blasts present in bone marrow and genetic changes associated with the disease.	

The following information and accompanying tables provide support for decision making related to Immunosuppression Category. Chemotherapeutic and other immunosuppressive agents, as well as corticosteroids (based upon dose and duration) have been classified according to their potential effect on immune status.

Effect of Treatment on Immune Status

Chemotherapeutic and Other Immunosuppressive Agents (Not Corticosteroids)

The following tables list chemotherapeutic agents according to their propensity to cause immunosuppression. In some cases, combining chemotherapeutic agents into a treatment regimen increases the risk/level of immunosuppression, therefore the decision on risk/level of immunosuppression for combined regimens should be determined on the basis of the drug with the highest propensity for immunosuppression.

Table 6-3

Immunosuppressive Effect/Classification of Chemotherapeutic and Other Agents

Immunosuppressive Effect				
None	Low	Moderate	High	Very High
Abarelix Anastrozole Bicalutamide Dexrazoxane Exemestane Flutamide Fulvestrant Goserelin GW572016 (lapatinib) Letrozole Leuprolide Megestrol Nilutamide Octreotide Acetate Octreotide Pamoate Oprelvekin Testolactone Toremifene Tamoxifen Triptorelin	Bevacizumab Cetuximab Erlotinib Gefitinib Hydroxyurea Lenograstim Megace Methoxsalen Mitotane Panitumumab Pegfilgrastim Rhumab VEGF Sargramostim (G-CSF) Sorafenib (Bay 43-9006) Sunitinib TevaGrastim Trastuzumab Vorinostat ZD1839	Abatacept Adalimumab Aldesleukin Aminoglutethimide Anakinra Arsenic trioxide Auranofin BCG live vaccine Bexarotene Bortezomib Dasatinib Eculizumab Imatinib Mesylate Interferon alfa-2A Interferon alfa-2B Interferon alfa-N3 Interferon beta-1A Interferon beta-1B Interferon gamma-1B Lenalidomide MAB-B43.13 Nilotinib Peginterferon alfa-2A Peginterferon alfa-2B Penicillamine Rituximab Thalidomide Tretinoin	Alimta Altretamine Asparaginase Azacitidine Bleomycin Busulfan Carboplatin Carmustine Chlorambucil Chronic or Na P-32 Cisplatin Cyclophosphamide Cytarabine Dacarbazine Dactinomycin Daunorubicin Decitabine Docetaxel Doxorubicin Epirubicin Estramustine Etoposide Floxadine Fluorouracil Gemcitabine Hexamethylmelamine Idarubicin Ifosfamide/mesna Irinotecan Ixabepilone Leflunomide Lomustine Mechlorethamine Melphalan Mercaptopurine Methotrexate Mitomycin Mitoxantrone Nelarabine Nitrogen Mustard Oxiplatin/Oxaliplatin Paclitaxel Pegaspargase Pemetrexed disodium (Alimta) Pipobroman Procarbazine Streptozocin Temozolomide Teniposide Thioguanine Thiotepa TLK286 Topotecan Trimetrexate Vinblastine Vincristine Vinorelbine	Alemtuzumab Antithymocyte Globulin Azathioprine Basiliximab Capecitabine Cladribine Ciclofarabine Cyclosporin Daclizumab Denileukin defitox Etanercept Fludarabine Gemtuzumab Ibritumomab Tiuxetan Infliximab Muromonab-CD3 Mycophenolate mofetil Pentostatin Sirolimus Tacrolimus Temsilolimus Tositumomab

Systemic Corticosteroid Therapy

Table 6-4 provides a list of corticosteroids for systemic and accompanying dosage and duration of treatment related to level of immunosuppression. Levels of immunosuppression are comparable to the levels listed in Table 6-3 and should be used to assist in the decision making relative to IC determination.

Table 6-4

Immunosuppressive Effect/Classification of Systemic Corticosteroids

Agent, Dose and Duration of Therapy	Cumulative dose	Level of Immunosuppression
<u>Systemic Corticosteroids, for > 14 days</u> Prednisone or prednisolone >20mg/d Hydrocortisone > 80 mg/day Methylprednisolone > 16 mg/day Dexamethasone > 3 mg/day (if Dexamethasone is given 10 mg once every 3 weeks for less than 6 months, it is considered mild IC – see category 4 below)	≥700 mg regardless of duration of treatment	Very high
<u>Systemic Corticosteroids, > 14 days</u> Prednisone 7.5-20 mg/day Prednisolone 7.5-20 mg/day Hydrocortisone 30-80 mg/d Methylprednisolone 6-16 mg/day Dexamethasone 1.125-3 mg/day	70-280 mg for ≥2 weeks or <700 mg regardless of duration of treatment	High
<u>Systemic Corticosteroids, for < 14 days</u> Prednisone or prednisolone > 7.5 mg/day Hydrocortisone > 30 mg/day Methylprednisolone > 6 mg/day Dexamethasone > 1.125 mg/day	<70mg for ≥2 weeks or 70-280 mg for <2weeks	Moderate
<u>Systemic Corticosteroids, regardless of duration:</u> Prednisone or prednisolone, < 7.5 mg/day Hydrocortisone, < 30 mg/day Methylprednisolone, < 6 mg/day Dexamethasone, < 1.125 mg/day Dexamethasone 10 mg once every 3 weeks	< 70 mg for less than 2 weeks	Mild

6.2 ADVERSE EXPERIENCE TOXICITY GRADING SCALE

A toxicity grading scale will be assigned to all clinical adverse experiences in this study. Table 6-5 and Table 6-6 outline the Toxicity Grading Scale for injection-site and systemic adverse experiences, respectively.

Table 6-5

Injection-Site AE Toxicity Grading Scale

Injection Site Reaction to Study Vaccine/Placebo*	Grade 1	Grade 2	Grade 3	Grade 4
Injection-site AEs occurring days 1 through 5 following receipt of study vaccine/placebo				
Pain/Tenderness	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Erythema/Redness	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Induration/Swelling	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or ER visit or hospitalization
Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Any injection-site reaction that begins ≥ 6 days after receipt of study vaccine/placebo				
Pain/tenderness Erythema/Redness Induration/Swelling Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
*Based upon information provided by the patient on the Vaccine Report Card (VRC) and verbally during VRC review. Erythema/Redness/Induration and Swelling are specific injection-site AEs with size designations of letters A through E→, based upon a graphic in the VRC. Size A is not assigned a toxicity grade; however, injection-site AEs that measure size A should be reported as adverse experiences. If the subject has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned a toxicity grade of 4, regardless of the size measured.				

Table 6-6

Systemic AE Toxicity Grading Scale

Systemic Illness*	Grade 1	Grade 2	Grade 3	Grade 4
Illness or clinical adverse experience (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and required medical intervention	Emergency room visit or hospitalization
<p>*Based upon information provided by the patient on the VRC and verbally during VRC review during the primary safety follow-up period. For SAEs reported beyond the primary safety follow-up period, grading will be based upon the initial report and/or follow-up of the event</p> <p>Note: Events determined to be life-threatening or resulting in death are also assigned a Toxicity Grade = 4.</p>				

6.3 INTERIM ANALYSIS PLAN STRATEGY

This section contains original text from V212-011-03 describing the plan for interim futility analyses (performed on 29-Oct-2014) and the interim efficacy analysis (which will not be conducted due to the futile outcome in the interim futility analysis in the HM arm and the risk of a false negative result due to the small number of cases in the STM arm).

2.4.1 Summary of Study Design (from V212-011-03)

The first interim (futility) analysis will be conducted when at least 50% of the total number of required confirmed HZ cases has accrued in each patient population, HM and STM. Depending on respective accrual rates of HZ cases in HM and STM patients, interim analysis may or may not be conducted at the same time for the 2 populations. Results of the analysis will be reviewed by the DMC, who will make recommendations to the Steering Committee (SC) to continue, modify, or end the study according to the following plan:

- If vaccine efficacy meets expectation with both populations, the study will continue with both populations according to the initial plan.
- If vaccine efficacy meets expectation with the HM population, but is lower than expected for the STM population,
 - o The study will be considered to have failed with the STM arm; the study will enter close-out phase for the STM arm; no additional HZ case will be accrued for the STM arm; all STM patients will be contacted to complete the study close-out questions.
 - o The study will continue with the HM arm only; the sample size will be increased for the HM population from 2568 to 6067 and the study will continue to accrue approximately 328 confirmed HZ cases.
- If vaccine efficacy meets expectation with the STM population, but is lower than expected for the HM population:
 - o The study will be considered to have failed with the HM arm; the study will enter close-out phase for the HM arm; no additional HZ case will be accrued for the HM arm; all HM patients will be contacted to complete the study close-out questionnaire.
 - o The study will continue with the STM arm only; the sample size for the STM population will be increased from 2696 to 5836 and the study will continue to accrue approximately 210 confirmed HZ cases.
- If vaccine efficacy is lower than expected in both populations, the study will be considered to have failed and will be terminated.

2.7.5 Interim Analysis (from V212-011-03)

There will be two interim analyses, and one final efficacy analysis. The purpose of the futility analysis at the first interim is to terminate the whole study or either subgroup population if vaccine efficacy is lower than expected. The purpose of the second interim analysis is to terminate the study if vaccine efficacy is much lower or higher than expected.

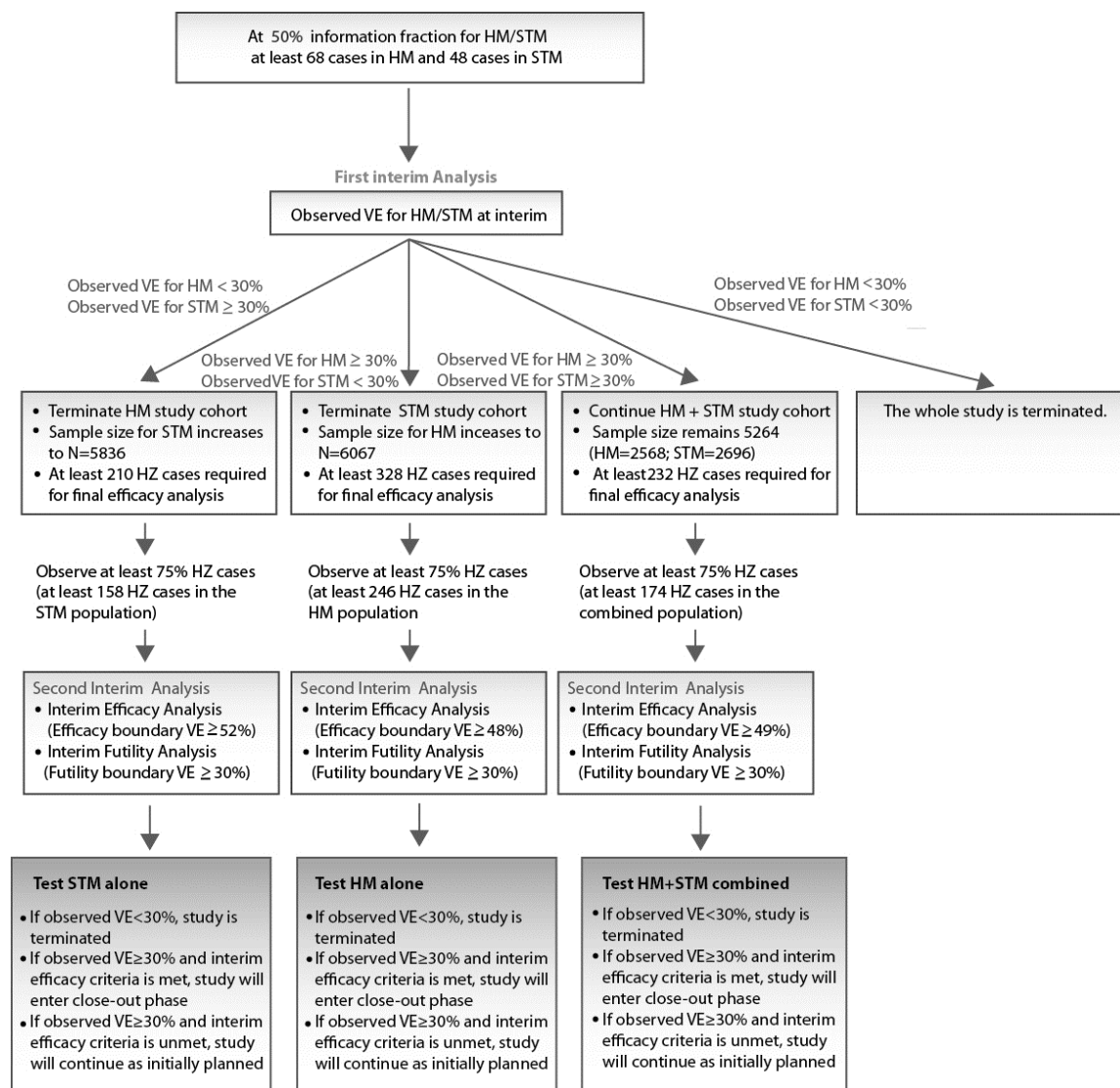
Table 2-3 and Figure 2-2 summarize the interim analysis strategy. Details regarding the interim analysis plan are specified in Section 3.5.8.1.

Table 2-3
Summary of Interim Analysis Strategy

Interim Analysis Number	Key Endpoints for Interim Analysis	Anticipated Timing of Interim Analysis	Purpose of Interim Analysis
First	<ul style="list-style-type: none"> incidence of HZ in the vaccine and placebo groups in HM and STM subgroup population individually 	<p>50% of the required confirmed cases of HZ in each individual population has accrued.</p> <ul style="list-style-type: none"> at least 68 cases have accrued for HM subgroup at least 48 cases have accrued for STM subgroup <p>Of note, the futility analysis for HM and STM populations may not be conducted concurrently</p>	<ul style="list-style-type: none"> Stop for futility Potential to stop one arm and enrich the population in the remaining arm
Second	<ul style="list-style-type: none"> incidence of HZ in the vaccine and placebo group 	<p>75% of the total number of required confirmed cases of HZ</p> <p>Total evaluable cases required at second interim:</p> <p>If move forward with <u>combined HM and STM</u></p> <ul style="list-style-type: none"> at least 174 cases (with a minimum of 64 and 95 confirmed HZ cases in the STM and HM populations, respectively) have accrued for combined population. <p>If move forward with <u>STM subgroup population alone</u></p> <ul style="list-style-type: none"> at least 158 cases have accrued for STM subgroup <p>If move forward with <u>HM subgroup population alone</u></p> <ul style="list-style-type: none"> at least 246 cases have accrued for HM subgroup <p>Of note: the second interim analysis will not be performed until the first interim analysis is completed on both populations. The second interim analysis may not be performed if, based upon the enrollment rate and the time to confirm the required number of HZ cases, either of the following scenarios occur: 1) timing of the first interim analyses in the individual subpopulations approximates the timing of accrual of the required 75% of the confirmed HZ cases that trigger the second interim analysis; 2) the study is nearing completion at the time the results of the second interim analysis would be available. In either of these scenarios, the final analysis may be performed in lieu of the second interim analysis.</p>	<ul style="list-style-type: none"> Stop for futility Stop for efficacy

Figure 2-2

Interim Analysis Flow Chart



3.5.8.1 Interim Analyses of Futility/ Efficacy for Potential Early Study Termination (from V212-011-03)

The first interim (futility) analysis will be done on the HM and STM populations when at least 50% of the total number of required evaluable cases of HZ in each individual population has accrued. More specifically, the first futility analysis will be done on the HM population and the STM population individually. When at least 68 cases have accrued in the HM population, the futility check on the HM population will be conducted; when at least 48 cases have accrued in the STM population, the futility check on the STM population will be conducted. It should be noted that this first futility analysis for the HM and STM population might not occur concurrently as one subgroup might accrue HZ cases in the speed much slower than expected.

Table 3-4 and Table 3-5 illustrate the probabilities to observe a VE lower than futility cutoff. The result indicated that given the true vaccine efficacy for HM and STM is as low as 25%, the probability to observe vaccine efficacy lower than 30% at first interim is about 0.560 and 0.620 for HM and STM respectively. The probability to terminate the whole study (both HM and STM) is $\approx 35\%$ when the true vaccine efficacy for HM and STM is as low as 25%.

Table 3-4

Probabilities to Observe a VE Lower than Futility Cutoff	
50% information fraction (68 HZ cases accrued for HM group)	
If TRUE VE=	Probability(interim_VE \leq 0.3)
0.20	0.661
0.25	0.560
0.30	0.448
0.35	0.333
0.40	0.225
0.50	0.069
50% information fraction (48 HZ cases accrued for STM group)	
0.20	0.701
0.25	0.620
0.30	0.527
0.35	0.427
0.40	0.324
0.50	0.142
0.55	0.078

Table 3-5

Probabilities the Trial will Stop Completely at First Interim Analysis

TRUE VE for STM	TRUE VE for HM	Prob(interim VE \leq 0.3)
0.20	0.20	0.463
0.25	0.25	0.347
0.30	0.30	0.236
0.35	0.35	0.142
0.40	0.40	0.073
0.50	0.50	0.010

Table 3-6 illustrates the overall type I error rate and power comparison based on the futility boundary and timepoints proposed for the first futility analysis. The result indicated that given futility boundary for observed vaccine efficacy to be 30% and 30% for the STM and HM populations at 50% information fraction, the overall power would be around 90% and type one error is controlled under 0.025. It also provided sufficient power (≈ 0.70) when one of the subgroups has much lower VE than expected.

Table 3-6

Overall Type I Error Rate and Power Comparison by Futility Boundary and Information Fraction for the First Futility Analysis

First futility analysis		Vaccine Efficacy assumed				
		VE_HM=25% VE_STM=25% (Type I error rate)	VE_HM=25% VE_STM=55% (Power)	VE_HM=50% VE_STM=25% (Power)	VE_HM=35% VE_STM=55% (Power)	VE_HM=50% VE_STM=55% (Power)
Futility boundary	Information fraction					
Ob_HM >30% Ob_STM >30%	40% (N_HM=54, N_STM=39)	0.025	0.655	0.660	0.718	0.928
	50% (N_HM=68, N_STM=48)	0.025	0.679	0.698	0.730	0.928
	60% (N_HM=81, N_STM=58)	0.028	0.703	0.721	0.743	0.930

For the first futility analysis, a conditional power approach will be used. More specifically, when at least 50% of the total number of required evaluable cases of HZ have accrued and if the point estimates of vaccine efficacy is no more than 30% and 30% for the STM and HM populations, respectively, then the study may be stopped due to futility since the conditional power (probability of having a successful trial) at the end of study would be <1% based on the observed information.

If the HM portion of the study is terminated and the STM portion of the study continues based the first futility analysis, the enrollment for the STM portion of the study will be increased from to 2596 to 5836 to accrue 210 HZ cases. If the STM portion of the study is terminated and the HM portion of the study continues based the first futility analysis, the enrollment for HM study will be increased from 2568 to 6067 to accrue 328 HZ cases. If the point estimate of the vaccine efficacy is no more than 30% in the HM interim futility analyses and the point estimate of the vaccine efficacy is no more than 30% in the STM interim futility, then the whole study may be stopped, i.e. if the vaccine efficacy is lower than expected in both populations, the study will be stopped.

The second futility interim analysis will be done together with the formal interim efficacy analysis when at least 75% of the total number of required evaluable cases has accrued. Of note, the population for this second futility interim and formal interim efficacy analysis depends on the decision made at the first futility interim analysis. The second interim analyses will not be performed until the first interim analysis is completed on both populations. The population for analysis can be (1) combined population (HM and STM) if both populations pass the futility check at interim; or (2) STM population alone if the HM portion of the study is terminated based on the futility interim analyses; or (3) HM population alone if the STM portion of the study is terminated based on the futility interim analyses. If the combined HM and STM population moves forward, to ensure that there is sufficient information for each population for the secondary hypotheses in the event that the study stops early for overwhelming efficacy, a minimum of ~70% of the targeted number of HZ cases in each population is also required for the 2nd interim analysis. That is at least 174 cases in combined population (with a minimum of 64 and 95 confirmed HZ cases in the STM and HM populations, respectively) is required for the second interim analysis. If the HM population only moves forward, at least 246 cases is required for second interim analysis. If STM population only moves forward, at least 158 cases is required for second interim analysis.

For the second futility analysis, a conditional power approach will be used similar to the first futility analysis. More specifically, when at least 75% of the total number of required evaluable cases have accrued and if the point estimate of the vaccine efficacy is no more than 30%, then the study may be stopped due to futility since the conditional power (probability of having a successful trial) at the end of study would be <0.1% based on the observed information.

The purpose of the interim efficacy analysis is to terminate the study if overwhelming efficacy is shown. Both the results from the per-protocol population and the modified intent-to-treat population have to meet the early stopping criteria in order to end the study early.

To control the overall Type I error at two-sided 0.05 level for the combined study or on each individual subgroup population, Hwang, Shih and DeCani (gamma family) α -spending function [53] with the parameter $\gamma = -3.5$ will be used for the interim monitoring. If

- (1) the primary hypothesis is tested on HM and STM populations combined given the vaccine efficacy for both populations exceed the futility boundary at interim, the type I errors spent and the corresponding 2-sided symmetric boundaries computed for the 2 looks are (0.02, 0.03) and (2.33, 2.02). The corresponding 2-sided nominal significance levels are 0.02, 0.044, respectively.
- (2) primary hypothesis is tested on a single subgroup population only given one subgroup fails at the futility check at interim, to control the overall Type I error at two-sided **0.023** level for the individual population (HM subgroup or STM subgroup), then the type I errors spent and the corresponding 2-sided symmetric boundaries computed for the 2 looks are 0.009, 0.014 and 2.61, 2.33. The corresponding 2-sided nominal significance levels are 0.009, and 0.020, respectively.

The lower bound of CIs for vaccine efficacy corresponding to these significance levels will be provided for study stopping criterion.

Of note, the 2nd interim analysis will not be performed until the 1st interim analysis is completed on both populations otherwise the decision on whether both populations should be moved forward could not have been made. To account for the potential change of information fraction, i.e. the second interim analysis might not occur at 75% information fraction, the test levels at the 2nd interim analysis and the final analysis will be adjusted. This adjustment would be updated based on the real information fraction at the 2nd interim analysis using the alpha-spending function specified in the protocol so that the overall type I error rate of the study will be controlled as planned.

An unblinded SPONSOR statistician who is otherwise unrelated to this protocol will serve as a non-voting member of DMC and will be responsible for performing the required analyses. The DMC will monitor safety closely and will be responsible for reviewing the planned formal interim analyses results. The DMC may recommend stopping the study early based on successful interim efficacy analysis results or safety concerns.

At the interim efficacy look when at least 75% of the total expected events have accrued, the DMC will consider stopping the study early for efficacy if the lower bound of the specified CIs on VE_{HZ} is $> 25\%$; otherwise, the study will continue. If the study terminates early for the primary endpoint efficacy at the interim look, the adjusted point estimate, CI and p-value from the interim analysis for the vaccine efficacy for HZ (VE_{HZ}) will be provided using stage-wise ordering [54, 55].

While the HZ cases will be monitored closely, at the time when the interim analysis actually occurs, the actual information might not be exactly the same as pre-specified as above. The corresponding type I error spent, 2-sided symmetric boundary and 2-sided nominal p-value to be used as the study stopping criteria at interim look will be updated with the actual information accordingly.

The power of the interim efficacy analysis depends upon the proportion of the required number of evaluable cases of HZ that is included in the analysis. When at least 75% of the total number of required evaluable cases has accrued and satisfactory efficacy is shown, the study has adequate power to claim success. The power (probability of having a successful trial) would be >0.9 if the observed vaccine efficacy is 60% at interim efficacy analysis for combined (HM+STM) population given both subgroups pass the futility check at interim. The power would be >0.83 if the observed vaccine efficacy is 60% at interim efficacy analysis for STM subgroup primary hypothesis is tested on HM subgroup population. The power would be >0.9 if the observed vaccine efficacy is 60% at interim efficacy analysis for HM subgroup given primary hypothesis is tested on HM subgroup population (Table 3-7).

Table 3-7

Power for Interim Efficacy Analysis at 75% Information Fraction

If primary hypothesis is tested on combined (HM+STM) population			
	Vaccine efficacy observed		
	VE=52%	VE=55%	VE=60%
Power	0.572	0.719	0.903
If primary hypothesis is tested on STM subgroup population			
	VE=55%	VE=60%	VE=65%
Power	0.603	0.828	0.956
If primary hypothesis is tested on HM subgroup population			
	VE=50%	VE=55%	VE=60%
Power	0.583	0.838	0.967

Table 3-8 lists the alpha spent, the critical value, and the nominal p-value for the analysis at the design stage. The values in this table will be updated based on the actual information from the data.

Table 3-8

Critical Values and Other Related Parameters at the Interim Efficacy and Final Analyses

	HM/STM combined study		Individual population HM/STM if one subgroup population fails at interim			
Alpha-spending Function	Hwang, Shih and DeCani (gamma family) ($\gamma = -3.5$)		Hwang, Shih and DeCani (gamma family) ($\gamma = -3.5$)			
Time Point	1 (interim analysis)	2 (final analysis)	1 (interim analysis)	2 (final analysis)		
Information Fraction (%)	75	100	75	100		
Alpha Spent	0.02	0.03	0.009	0.014		
Critical Value	2.33	2.02	2.61	2.33		
2-sided Nominal p-Value	0.02	0.044	0.0092	0.0196		
Population	Combined		STM	HM	STM	HM
Maximum numbers of cases allowed in the vaccine group	59	83	51	84	72	119
Minimum numbers of cases required in the placebo group	115	149	107	162	138	209
Estimated VE_{HZ}	0.49	0.44	0.52	0.48	0.48	0.43

If the study terminates early for the primary endpoint efficacy at the interim look, the adjusted point estimate, CI and p-value from the interim analysis for VE_{HZ} will be provided using stage-wise ordering [54, 55]. To evaluate the utility of the immune markers, the key immunogenicity endpoints will also be analyzed in the interim analysis according to the plan specified in Section 3.5.5.2. A CSR may be written and submitted to regulatory agencies based on the data available up to the time point of data frozen for the interim look. The decision to stop the study and end enrollment will be made by the Steering Committee, based on the recommendation of the DMC.

In the event that the study terminates early at the interim analysis and the CSR is written for regulatory submission, for those patients that are still in their 1 year safety and efficacy follow-up or those HZ cases that are still in their 6-month follow-up at the time when the data was frozen for the interim analyses, the remaining endpoints will continue to be collected until the minimum 1 year postvaccination safety and efficacy follow-up is completed for all patients and all suspected HZ cases complete their 6-month follow-up. Data collected from the remaining study follow-up time and the corresponding analysis results will be provided in a supplemental summary document, as needed. Under this scenario, the SPONSOR personnel directly involved in the study, investigators, site personnel, clinical adjudicators, and patients will remain blinded until the end of the study (i.e., until final database lock), while a separate unblinded team of SPONSOR personnel not involved in the data review and data cleaning of the ongoing study will be responsible for authoring the CSR.

7. ATTACHMENTS

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."

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME

SIGNATURE

DATE

8.2 INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study 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 experiences as defined in the SAFETY MEASUREMENTS section of this protocol. 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 study 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

SIGNATURE

DATE