2 SYNOPSIS

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	V212 varicella-zoster virus vaccine inactivated (Oka/Merck) Injection	
INDICATION:	Prophylaxis	
PROTOCOL TITLE:	A Phase II Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Immunogenicity of V212 in Adult Patients with Autoimmune Disease	
TRIAL IDENTIFIERS:	Protocol Number:	009
	Clinical Phase:	2
	EudraCT Number:	
	ISRCT number:	
TRIAL CENTERS:	This trial was conducted at 62 trial centers: 20 in the United States; 30 in Europe; 3 in Australia; 5 in Latin America; and 4 in Canada.	

DESIGN:	This was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and immunogenicity of V212 in adults with autoimmune disease. Approximately 340 patients ≥18 years of age were planned to be randomized, via an Interactive Voice Response System, to receive a 4-dose regimen of either V212 (~180 recipients), V212 with a higher quantity of antigen (Ag) (~100 recipients) or placebo (~60 recipients). Randomization was stratified by baseline autoimmune treatment regimen: ~170 patients receiving at least one biologic agent, with or without non-biologic therapy; and ~170 patients receiving at least one non-biologic therapy but no biologic agents (~90 V212 recipients, ~50 recipients of V212 with a higher quantity of Ag, ~30 placebo recipients in each of the two strata). Enrollment for this study was expected to be completed in approximately 12 months. Daily oral temperature readings and injection-site and systemic adverse experiences occurring from Day 1 through 28 days Postdose 4 were recorded on a Vaccination Report Card (VRC). Patients were actively prompted to record on the VRC injection-site adverse experiences for 5 days after each vaccination dose. The VRC was reviewed by study site personnel at the end of the follow-up period following each vaccination dose. All patients were followed for exposure to varicella or herpes zoster (HZ) and development of any varicella/varicella-like or HZ/HZ-like rashes, or other symptoms suggestive of HZ through 28 days Postdose 4. Patients who developed suspected varicella/varicella-like or HZ/HZ-like rashes during the follow-up period through 28 days Postdose 4 were instructed to contact the investigator to be seen as soon as possible after rash onset (preferably within 24 to 72 hours) for clinical evaluation and the collection of lesion swabs for polymerase chain reaction (PCR) analysis. Serum samples to measure varicella-zoster virus (VZV) antibody concentrations by glycoprotein enzyme-linked immunosorbent assay (gpELISA), and whole blood samples to detect interferon-gamma (IFN-γ)-secreting VZV-specific cell responses from peripheral blood mononuclear cells (PBMCs) via IFN-γ enzyme-linked immunospot (ELISPOT), were collected from all patients on Day 1 (prior to Dose 1) and at Visit 5 (~Day 118, 28 to 35 days Postdose 4). Additionally, one half of the study population (~170 patients) was assigned to have blood collected at Visit 3 (~Day 60, 21 to 35 days Postdose 2), and the other half of the population (~170 patients) was assigned to have blood collected at Visit 4 (~Day 90, 21 to 35 days Postdose 3).	
	Planned duration of main phase:	There were ~30 days between the administration of study vaccine Doses 1 through 4, and 28 days of safety follow-up Postdose 4.
	Planned duration of run-in phase:	Not applicable
	Planned duration of extension phase:	Not applicable
Objectives	(1) To determine whether V212 is immunogenic when administered to adult patients with autoimmune disease. (2) To assess the safety and tolerability of V212 in adult patients with autoimmune disease.	
Hypotheses	V212 will elicit significant VZV-specific immune responses measured by either gpELISA or IFN-γ ELISPOT at approximately 28 days Postdose 4 in adults with autoimmune disease. The statistical criterion corresponds to the lower bound of the two-sided 95% confidence interval (CI) on the geometric mean fold rise (GMFR) in the vaccine recipients being >1.0. The primary approach on immunogenicity was based on the per-protocol population. There will be no formal safety hypothesis.	

Vaccination groups	V212	Target Potency: [redacted] UAg (Units of Antigen) per 0.5-mL Dose Subcutaneous injection 4-Dose regimen, ~30 days apart 190 patients
	V212 containing a higher quantity of Ag	Target Potency: [redacted] UAg (Units of Antigen) per 0.5-mL Dose Subcutaneous injection 4-Dose regimen, ~30 days apart 102 patients
	Placebo	Target Potency: Not Applicable 0.5-mL Subcutaneous injection 4-dose regimen, ~30 days apart 62 patients

Clinical Supplies Administered to Patients

Product	Dosage Form	Formulation Numbers	Potency (UAg/0.5-mL Dose)
V212	Lyophilized Powder for Subcutaneous Injection	[redacted]	[redacted]
V212	Lyophilized Powder for Subcutaneous Injection		
V212	Lyophilized Powder for Subcutaneous Injection		
V212 containing a higher quantity of Ag	Lyophilized Powder for Subcutaneous Injection		
Placebo	Lyophilized Powder for Subcutaneous Injection		N/A
Sterile Diluent for reconstitution of vaccines (sterile water)	Sterile solution		0.7 mL (fill volume)

UAg = Units of Antigen.
mL = milliliter.
N/A = Not applicable.

Endpoints and definitions	Primary immunogenicity endpoint		For immune responses measured by gpELISA or VZV IFN-γ ELISPOT, the primary immunogenicity endpoint was the GMFR of the VZV-specific immune responses from prevaccination to 28 days Postdose 4.
	Primary safety endpoint		The primary safety endpoint was based on the incidence of serious adverse experiences observed during the four follow-up periods in each of the two vaccination groups (i.e., the Pooled vaccine group and the placebo group).
	Other key endpoints		Other key endpoints include the GMFR and the geometric mean titer (GMT) or geometric mean count (GMC) at Postdose 2 (Visit 3), Postdose 3 (Visit 4), as well as the GMT and GMC at ~28 days Postdose 4 (Visit 5) within each group.
Database lock	14-JUN-2013	Trial status: Completed	06-MAR-2012: First patient first visit 26-FEB-2013: Last patient last visit
RESULTS AND ANALYSIS:	All analyses for safety and immunogenicity were performed according to the protocol.		

Disposition of Patients
By All Three Vaccination Groups - All Patients Randomized

	V212		V212 Higher Antigen		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized							8	
Patients in population	190		102		62		354	
Vaccinated at								
Vaccination 1	189	(99.5)	102	(100.0)	62	(100.0)	353	(99.7)
Vaccination 2	187	(98.4)	96	(94.1)	61	(98.4)	344	(97.2)
Vaccination 3	184	(96.8)	94	(92.2)	58	(93.5)	336	(94.9)
Vaccination 4	183	(96.3)	94	(92.2)	58	(93.5)	335	(94.6)
Study Disposition								
Completed	183	(96.3)	94	(92.2)	58	(93.5)	335	(94.6)
Discontinued	7	(3.7)	8	(7.8)	4	(6.5)	19	(5.4)
Adverse Event	3	(1.6)	2	(2.0)	0	(0.0)	5	(1.4)
Lost To Follow-Up	1	(0.5)	2	(2.0)	0	(0.0)	3	(0.8)
Physician Decision	2	(1.1)	0	(0.0)	0	(0.0)	2	(0.6)
Pregnancy	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)
Protocol Violation	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)
Screen Failure	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.3)
Subject Moved	0	(0.0)	0	(0.0)	1	(1.6)	1	(0.3)
Withdrawal By Subject	0	(0.0)	2	(2.0)	3	(4.8)	5	(1.4)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.

Data Source: [16.4]

Patient Characteristics
All Patients Randomized - By All Three Vaccination Groups

	V212		V212 Higher Antigen		Placebo	
	n	(%)	n	(%)	n	(%)
Patients in population	190		102		62	
Gender						
Male	66	(34.7)	37	(36.3)	25	(40.3)
Female	124	(65.3)	65	(63.7)	37	(59.7)
Age (Years)						
18 to 49	79	(41.6)	39	(38.2)	27	(43.5)
50 to 59	57	(30.0)	32	(31.4)	14	(22.6)
60 to 69	41	(21.6)	24	(23.5)	12	(19.4)
70 to 79	13	(6.8)	7	(6.9)	6	(9.7)
80 +	0	(0.0)	0	(0.0)	3	(4.8)
Mean	51.8		52.2		52.9	
SD	12.1		12.4		14.8	
Median	51.0		54.0		56.0	
Range	20 to 78		23 to 79		25 to 87	
Race						
Asian	2	(1.1)	2	(2.0)	0	(0.0)
Black Or African American	15	(7.9)	8	(7.8)	5	(8.1)
Multiple	23	(12.1)	3	(2.9)	8	(12.9)
White	150	(78.9)	89	(87.3)	49	(79.0)
Ethnicity						
Hispanic Or Latino	33	(17.4)	10	(9.8)	9	(14.5)
Not Hispanic Or Latino	156	(82.1)	92	(90.2)	53	(85.5)
Unknown	1	(0.5)	0	(0.0)	0	(0.0)
Autoimmune treatment regimen						
Biologic Agents	87	(45.8)	55	(53.9)	28	(45.2)
Non-Biologic Therapy	103	(54.2)	47	(46.1)	34	(54.8)
Primary diagnosis						
Ankylosing Spondylitis	1	(0.5)	2	(2.0)	1	(1.6)
Aphthous Stomatitis	1	(0.5)	0	(0.0)	0	(0.0)
Autoimmune Arthritis	1	(0.5)	0	(0.0)	0	(0.0)
Autoimmune Hepatitis	2	(1.1)	1	(1.0)	1	(1.6)
Basedow's Disease	0	(0.0)	1	(1.0)	0	(0.0)
Behcet's Syndrome	0	(0.0)	1	(1.0)	0	(0.0)
Biliary Cirrhosis Primary	3	(1.6)	0	(0.0)	0	(0.0)
Cerebral Sarcoidosis	0	(0.0)	0	(0.0)	1	(1.6)
Colitis Ulcerative	6	(3.2)	2	(2.0)	2	(3.2)
Connective Tissue Disorder	1	(0.5)	1	(1.0)	0	(0.0)

Patient Characteristics
All Patients Randomized - By All Three Vaccination Groups

	V212		V212 Higher Antigen		Placebo	
	n	(%)	n	(%)	n	(%)
Primary diagnosis						
Crohn's Disease	19	(10.0)	7	(6.9)	7	(11.3)
Cutaneous Lupus Erythematosus	0	(0.0)	0	(0.0)	1	(1.6)
Dermatomyositis	1	(0.5)	0	(0.0)	0	(0.0)
Granulomatosis With Polyangiitis	0	(0.0)	1	(1.0)	1	(1.6)
Idiopathic Pulmonary Fibrosis	2	(1.1)	0	(0.0)	0	(0.0)
Interstitial Lung Disease	2	(1.1)	1	(1.0)	0	(0.0)
Mixed Connective Tissue Disease	0	(0.0)	1	(1.0)	2	(3.2)
Multiple Sclerosis	21	(11.1)	13	(12.7)	2	(3.2)
Myasthenia Gravis	3	(1.6)	0	(0.0)	1	(1.6)
Overlap Syndrome	0	(0.0)	0	(0.0)	1	(1.6)
Pemphigus	0	(0.0)	1	(1.0)	0	(0.0)
Polyarteritis Nodosa	1	(0.5)	0	(0.0)	0	(0.0)
Polymyalgia Rheumatica	0	(0.0)	1	(1.0)	0	(0.0)
Polymyositis	2	(1.1)	1	(1.0)	1	(1.6)
Psoriasis	36	(18.9)	25	(24.5)	13	(21.0)
Psoriatic Arthropathy	5	(2.6)	4	(3.9)	0	(0.0)
Pulmonary Fibrosis	0	(0.0)	0	(0.0)	1	(1.6)
Rheumatoid Arthritis	55	(28.9)	31	(30.4)	17	(27.4)
Sarcoidosis	1	(0.5)	0	(0.0)	0	(0.0)
Scleroderma	1	(0.5)	1	(1.0)	0	(0.0)
Sjogren's Syndrome	1	(0.5)	1	(1.0)	0	(0.0)
Still's Disease Adult Onset	0	(0.0)	0	(0.0)	1	(1.6)
Systemic Lupus Erythematosus	23	(12.1)	6	(5.9)	8	(12.9)
Undifferentiated Connective Tissue Disease	0	(0.0)	0	(0.0)	1	(1.6)
Vasculitis	2	(1.1)	0	(0.0)	0	(0.0)

Analysis description	**Immunogenicity**
Analysis Plan	The primary immunogenicity analysis population was the per-protocol population of the V212 group (excluding the V212 with a higher quantity of antigen group). The immunogenicity endpoints were the GMT (or GMC) and GMFR of the VZV-specific immune responses measured by VZV gpELISA and VZV IFN-γ ELISPOT, from prevaccination to ~28 days Postdose 4. The primary immunogenicity hypothesis is H0: $GMFR_V \leq 1.0$ versus H1: $GMFR_V > 1.0$, where $GMFR_V$ is the GMFR at ~28 days Postdose 4 among V212 recipients. This hypothesis was tested for both VZV gpELISA and VZV IFN-γ ELISPOT. Hypothesis testing and estimation for each assay was based on a longitudinal model using data from the V212 group, with the log-transformed VZV responses at each visit being used as response variables and the visit variable and stratification factor as covariates, with an unstructured covariance structure. As a supportive analysis to the hypothesis testing, the fold-differences between the V212 and placebo groups and 95% CI were estimated at ~28 days Postdose 4 using a longitudinal regression model. For each assay, the raw observed GMT or GMC, and GMFR in each vaccination group at each available time point were summarized.

Summary	V212 elicited statistically significant VZV-specific immune responses measured by either gpELISA or VZV IFN-γ ELISPOT at 28 days Postdose 4. The estimated GMFR of the VZV-specific antibody response measured by gpELISA at ~28 days Postdose 4 was 1.57 (95% CI: 1.44 to 1.72). The estimated GMFR of the VZV-specific cell-mediated immune response measured by IFN-γ ELISPOT at ~28 days Postdose 4 was 2.01 (95% CI: 1.57 to 2.58). [redacted]

Statistical Analysis of VZV gpELISA Responses at ~28 Days Post Dose 4 and Other Time Points among V212 Recipients (Per-Protocol Population)

Endpoint	V212 (N=189)		p-Value
	n	Estimated Response† (95% CI)	
21-35 Days Post Dose 2			
GMT	176	279.78 (240.48, 325.50)	
Geometric Mean Fold Rises from Day 1	176	1.36 (1.25, 1.48)	
21-35 Days Post Dose 3			
GMT	176	337.75 (292.21, 390.39)	
Geometric Mean Fold Rises from Day 1	176	1.64 (1.51, 1.79)	
21-35 Days Post Dose 4			
GMT	176	324.37 (280.16, 375.56)	
Geometric Mean Fold Rises from Day 1	176	1.57 (1.44, 1.72)	<0.0001

† Calculated based on a single longitudinal regression model adjusting for prevaccination values.

N=Number of patients vaccinated in each group.

n = Number of patients contributing to this immunogenicity analysis (having valid results at baseline or the time points post baseline).

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

GMT = Geometric Mean Titer.

CI = Confidence interval.

VZV = Varicella-zoster virus.

Statistical Analysis of VZV IFN-γ ELISPOT Responses at ~28 Days Post Dose 4 and Other Time Points among V212 Recipients
(Per-Protocol Population)

Endpoint	V212 (N=189)		p-Value
	n	Estimated Response† (95% CI)	
21-35 Days Post Dose 2			
GMC	176	78.66 (59.12, 104.65)	
Geometric Mean Fold Rises from Day 1	176	2.24 (1.71, 2.93)	
21-35 Days Post Dose 3			
GMC	176	56.08 (37.82, 83.16)	
Geometric Mean Fold Rises from Day 1	176	1.60 (1.06, 2.41)	
21-35 Days Post Dose 4			
GMC	176	70.74 (54.80, 91.31)	
Geometric Mean Fold Rises from Day 1	176	2.01 (1.57, 2.58)	<0.0001

† Calculated based on a single longitudinal regression model adjusting for prevaccination values.

N=Number of patients vaccinated in each group.

n = Number of patients contributing to this immunogenicity analysis (having valid results at baseline or the time points post baseline).

IFN-γ ELISPOT = Interferon-gamma enzyme-linked immunospot assay.

GMC = Geometric Mean Count.

CI = Confidence interval.

VZV = Varicella-zoster virus.

Analysis description	**Safety**
Analysis Plan	All patients who received at least one dose of vaccine and had any safety follow-up were included in the safety evaluation, regardless of protocol deviations. The primary safety endpoint of the study was based on the incidence of serious adverse experiences observed during the four follow-up periods in each of the two vaccination groups (i.e., the pooled vaccine group and the placebo group). The two-sided 95% CI on the proportion of patients with any serious adverse experience were provided for each vaccination group based on the exact binomial distribution. To provide an overall assessment, the risk differences on the following safety parameters between the two vaccination groups (i.e., the pooled vaccine group and the placebo group) and the corresponding two-sided 95% CI on the risk difference were provided using the asymptotic methods proposed by Miettinen and Nurminen: the proportion of patients with (1) any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any vaccine-related serious adverse experience, and (5) any discontinuation due to an adverse experience for each of the pooled vaccine group and the placebo group (across any vaccination dosing period and by each vaccination dosing period).

Summary	Adverse experiences were reported for 75.1% of Pooled V212 recipients and 53.2% of placebo recipients. Injection-site adverse experiences were reported at a higher frequency in the Pooled V212 group (56.7%) compared with the placebo group (21.0%). All injection-site adverse events were considered vaccine-related. [redacted] The most frequently reported injection-site adverse events were erythema, pain and swelling in the Pooled V212 group, and pain in the placebo group. No statistically significant difference in the frequency of systemic adverse experiences was observed in the Pooled V212 group compared with the placebo group. The most frequently reported systemic adverse experiences were headache (6.9%), nasopharyngitis (5.9%), and pyrexia (4.5%) in the Pooled V212 group, and upper respiratory tract infection (6.5%) and rash (4.8%) in the placebo group. The incidence of systemic adverse experiences generally decreased with subsequent vaccine doses. The reported events and their observed frequencies were not unexpected based on the age of the population, the underlying medical conditions, and the therapies received. Ten patients reported 12 rashes of interest (5 varicella-like, 4 HZ-like and 3 HZ rashes). There were no statistically significant differences observed between the two groups for any of the VZV-like rashes. Vaccine strain VZV was not detected in any of the rash samples. During the protocol-specified safety follow-up period, 11 serious adverse experiences were reported among 9 study participants. A greater number of Pooled V212 recipients experienced a serious adverse experience (8) compared with the placebo recipients (1), although the overall serious adverse experience incidence rates in the two vaccination groups were similar. Two events (keratitis and amnesia) in the Pooled V212 group were determined by the investigator to be vaccine-related. One patient had a fatal serious adverse event (respiratory distress); this event was not assessed as vaccine-related by the investigator. A total of 5 vaccine recipients discontinued the study due to non-fatal adverse events. For three of the patients, the adverse events met serious criteria (diffuse B-cell lymphoma, breast cancer, and amnesia) and for two patients the adverse events were non-serious (swelling and erythema at the injection site, and myalgia). Of these events leading to discontinuation, the serious adverse event of amnesia and the non-serious adverse events of injection site swelling, injection site erythema, and myalgia were assessed by the investigator as vaccine-related. No safety concerns were identified; the results demonstrated that the V212 vaccine was generally well tolerated in this study population.

Analysis of Adverse Event Summary
Post Any Dose Through 28 Days Post Dose 4

	Pooled V212 Recipients		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population with follow-up	289		62		
with one or more adverse events	217	(75.1)	33	(53.2)	21.9 (8.9, 35.1)
injection site	164	(56.7)	13	(21.0)	35.8 (22.9, 46.1)
non-injection site	149	(51.6)	29	(46.8)	4.8 (-8.8, 18.1)
with no adverse events	72	(24.9)	29	(46.8)	-21.9 (-35.1, -8.9)
with vaccine-related[‡] adverse events	170	(58.8)	17	(27.4)	31.4 (18.0, 42.7)
injection site	164	(56.7)	13	(21.0)	35.8 (22.9, 46.1)
non-injection site	27	(9.3)	6	(9.7)	-0.3 (-10.6, 6.3)
with serious adverse events	8	(2.8)	1	(1.6)	1.2 (-5.9, 4.2)
with serious vaccine-related adverse events	2	(0.7)	0	(0.0)	
who died	1	(0.3)	0	(0.0)	
discontinued[§] due to an adverse event	5	(1.7)	0	(0.0)	
discontinued due to a vaccine-related adverse event	3	(1.0)	0	(0.0)	
discontinued due to a serious adverse event	3	(1.0)	0	(0.0)	
discontinued due to a serious vaccine-related adverse event	1	(0.3)	0	(0.0)	

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the vaccine.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

CONCLUSIONS:	In patients ≥18 years of age with autoimmune disease receiving biologic agents and/or non-biologic therapy and administered a 4-dose regimen of V212: 1. V212 elicited statistically significant VZV-specific immune responses measured by either gpELISA or VZV IFN-γ ELISPOT at 28 days Postdose 4. The lower bounds of the two-sided 95% CIs on the GMFR based on both gpELISA and IFN-γ ELISPOT assays in the vaccine recipients were >1.0. The pre-specified primary success criteria were met for immunogenicity. 2. V212 was generally well tolerated.