2 SYNOPSIS

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	V114, investigational 15-valent, pneumococcal conjugate vaccine (PCV 15), sterile liquid	
INDICATION:	Prevention of pneumococcal disease	
PROTOCOL TITLE:	A Multicenter, Double-Blind Study of the Safety, Tolerability, and Immunogenicity of a Pneumococcal Conjugate Vaccine (V114) Compared to Pneumococcal Polysaccharide Vaccine (PNEUMOVAX™ 23) and Prevnar 13™ (Pneumococcal 13-Valent Conjugate Vaccine [Diphtheria CRM197 Protein]) in Healthy Adults 50 Years of Age or Older	
TRIAL IDENTIFIERS:	Protocol Number:	002
	Clinical Phase:	2
	EudraCT Number:	2011-004542-18
TRIAL CENTERS:	This trial was conducted at 25 trial centers: 10 in the United States; 2 in Canada; 2 in Denmark; 2 in Israel; 2 in Norway, 3 in Poland, 2 in Spain and 2 in Sweden.	

DESIGN:	This was a randomized, double-blind (with in-house blinding procedures), active control multicenter Phase II study to compare the safety, tolerability, and immunogenicity profiles of a single dose of V114, PNEUMOVAX™ 23, or Prevnar 13™ in adults 50 years of age or older. Prevnar 13™ was selected as an active comparator because it is another PCV currently being evaluated for use in adults. Since Prevnar 13™ was only approved for use in children in most countries at the time of trial conduct, the use of Prevnar 13™ in the current study was investigational. Subjects were randomly assigned to 1 of 3 vaccination groups (approximately 230 subjects/group): V114, PNEUMOVAX™ 23, or Prevnar 13™ . Subjects were stratified by age at the time of randomization. In each vaccination group, ~1/3 of the subjects were 50 to 64 years of age, ~1/3 of the subjects were 65 to 74 years of age, and ~1/3 of the subjects were 75 years of age or older. Injection-site reactions and systemic adverse experiences were collected for 14 days postvaccination. Solicited adverse experiences were recorded by each subject on a validated vaccination report card (VRC) and included injection-site adverse experiences (swelling, redness, pain/tenderness, and hard lump) occurring on Days 1 through 5 and systemic adverse experiences (i.e., muscle pain, joint pain, headache, and tiredness) occurring on Days 1 through 14. Unsolicited adverse experiences were collected on the VRC for Days 1 through 14 following vaccination. Body temperature was measured orally for 5 days postvaccination and collected on the VRC. Serious adverse experiences were collected beginning when the informed consent was signed through 6 months postvaccination. Serum samples collected on Day 1 prior to vaccination and on Day 30 postvaccination were assayed for vaccine-induced immune responses to the 15 serotypes contained in V114. The serotype-specific IgG responses as measured using the pneumococcal electrochemiluminescence (Pn ECL) assay were used as the primary outcome measure. Serotype-specific opsonophagocytic activity (OPA) using the multiplex opsonophagocytic activity (MOPA-4) were assayed as a secondary objective	
	Planned duration of main phase:	1 day
	Planned duration of run-in phase:	not applicable
	Planned duration of extension phase:	not applicable

Objectives	Primary Objectives: (1) To demonstrate that the safety profile of a single dose of V114 is acceptable. (2) To compare serotype-specific IgG geometric mean concentrations (GMCs), as measured by Pn ECL assay between recipients of a single dose of V114 and a single dose of PNEUMOVAX™ 23 for the 14 shared serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F), as measured at 1 month postvaccination. Secondary Objective: Compare GMTs by MOPA-4 for the 14 serotypes in common between recipients of a single dose of V114 and a single dose of PNEUMOVAX™ 23 at one month postvaccination.	
Hypotheses	Primary Hypothesis: The serotype-specific GMCs as measured by the Pn ECL assay (adjusted for baseline IgG level) at one month postvaccination in subjects who receive V114 will be noninferior to those measured in subjects who receive PNEUMOVAX™ 23. (The statistical criterion corresponds to the lower bound of the two-sided 95% confidence interval (CI) on the Pn ECL GMC ratio [V114 / PNEUMOVAX™ 23] being > 0.5 for all 14 common serotypes.) Secondary Hypothesis: The GMT of the OPA responses at one month postvaccination in subjects who receive V114 will be noninferior to those in subjects who receive PNEUMOVAX™ 23. (The statistical criterion corresponds to the lower bound of the two-sided 95% CI on the OPA GMT ratio [V114 / PNEUMOVAX™ 23) being >0.33 for all 14 common serotypes.)	
Treatments groups	V114	2.0 µg per serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, 33F except 4.0 µg for serotype 6B, A single 0.5mL intramuscular injection on Day 1 230 Subjects
	PNEUMOVAX™ 23	25 µg per serotype 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F A single 0.5mL intramuscular injection on Day 1 231 Subjects
	Prevnar 13™	2.2 µg per serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F, except 4.4 µg for serotype 6B A single 0.5mL intramuscular injection on Day 1 230 Subjects

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
VAIV V110, PNEUMOVAX 23, 575 ug/vial, 0.5 mL, Pneumococcal Vaccine Polyvalent, Market Unlabeled	WL00045839, WL00046835
VSUS Pneumococcal 13-valent Conjugate Vaccine (PREVNAR 13) 0.5ml Syringe, 10 Count Package (ex-CAN)	WL00046564
VSUS Pneumococcal 13-valent Conjugate Vaccine (PREVNAR 13) 0.5ml Syringe, 10 Count Package (ex-US)	WL00045497
VSUS Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)(PREVENAR 13) 0.5ml Syringe,	DL00017323
VSUS V114, 64 ug/mL, 0.5 mL (0.25 mg/mL MAPA)	WL00044551

Endpoints and definitions	Primary immunogenicity endpoint		The primary immunogenicity endpoint was the serotype-specific IgG GMCs as measured by Pn ECL assay, for recipients of a single dose of V114 and a single dose of PNEUMOVAX™ 23 for the 14 shared serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F), as measured at 1 month postvaccination.
	Secondary immunogenicity endpoint		The secondary immunogenicity endpoint was the serotype-specific OPA GMTs as measured by MOPA-4 assay, for recipients of a single dose of V114 and a single dose of PNEUMOVAX™ 23 for the 14 shared serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F), as measured at 1 month postvaccination.

	Primary safety endpoint		Key safety measures for an overall assessment of safety include proportions of subjects with (1) any adverse experience, (2) any injection-site adverse experience, (3) any systemic adverse experience, (4) any serious adverse experience through 6 months postvaccination, (5) any vaccine-related serious adverse experience through 6 months postvaccination, and (6) any discontinuation due to an adverse experience. Other key safety parameters include proportions of subjects reporting the following solicited adverse experiences: injection-site swelling, redness, pain/tenderness, and hard lump occurring Days 1 to 5 postvaccination, and systemic adverse experiences of muscle pain, joint pain, headache, and tiredness occurring Days 1 to 14 postvaccination.
Database lock	25-OCT-2013	Trial status: Completed	19-MAR-2012 First subject first visit to 15-FEB-2013 Last subject last visit
RESULTS AND ANALYSIS:	All analyses for safety and immunogenicity were performed according to the protocol.		

Subject Characteristics

	V114		PNEUMOVAX 23		Prevnar 13		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	230		231		230		691	
Gender								
Male	108	(47.0)	108	(46.8)	108	(47.0)	324	(46.9)
Female	122	(53.0)	123	(53.2)	122	(53.0)	367	(53.1)
Age (Years)								
50 to 64	79	(34.3)	80	(34.6)	80	(34.8)	239	(34.6)
65 to 74	75	(32.6)	76	(32.9)	74	(32.2)	225	(32.6)
>= 75	76	(33.0)	75	(32.5)	76	(33.0)	227	(32.9)
Mean	68.0		67.8		68.1		68.0	
SD	9.3		9.6		9.8		9.5	
Median	67.5		67.0		68.0		68.0	
Range	50 to 91		50 to 88		50 to 90		50 to 91	

Race								
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Asian	5	(2.2)	6	(2.6)	3	(1.3)	14	(2.0)
Black Or African American	10	(4.3)	6	(2.6)	12	(5.2)	28	(4.1)
Multiple	3	(1.3)	2	(0.9)	0	(0.0)	5	(0.7)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.3)
White	212	(92.2)	217	(93.9)	212	(92.2)	641	(92.8)
Ethnicity								
Hispanic Or Latino	14	(6.1)	20	(8.7)	14	(6.1)	48	(6.9)
Not Hispanic Or Latino	216	(93.9)	211	(91.3)	215	(93.5)	642	(92.9)
Unknown	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)

Disposition of Subjects

	V114		PNEUMOVAX 23		Prevnar 13		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	230		231		230		691	
Trial Disposition								
Completed	226	(98.3)	225	(97.4)	226	(98.3)	677	(98.0)
Discontinued	4	(1.7)	6	(2.6)	4	(1.7)	14	(2.0)
Death	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.1)
Lost To Follow-Up	3	(1.3)	5	(2.2)	2	(0.9)	10	(1.4)
Withdrawal By Subject	1	(0.4)	0	(0.0)	2	(0.9)	3	(0.4)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.								

Analysis description	**Primary ImmunogenicityAnalysis** For the primary immunogenicity hypothesis, V114 was considered noninferior to PNEUMOVAX™ 23 if the lower bound of the two-sided 95% CI of the IgG GMC ratio (V114 / PNEUMOVAX™ 23) as measured by Pn ECL assay at one month postvaccination was no lower than 0.5 (non-inferiority margin) for serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F. Since the overall success of the study required demonstrating success on all 14 serotypes included in the primary immunogenicity hypothesis (which controls the overall alpha at 0.025, 1-sided), no other multiplicity adjustment was made.
	For the secondary immunogenicity hypothesis, V114 will be considered noninferior to PNEUMOVAX™ 23 if the lower bound of the two-sided 95% CI of the MOPA-4 GMT ratio (V114 / PNEUMOVAX™ 23) at one month postvaccination is no lower than 0.33 (non-inferiority margin) for serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F.

Analysis population and time point description	The Per-Protocol (PP) population served as the primary population for the analysis of immunogenicity data in this study. The PP population consists of those subjects who are not considered protocol violators. Immunogenicity measurements were taken prevaccination and 30 days post-vaccination.
Summary	V114 was non-inferior (using a 2-fold margin) to PNEUMOVAX™ 23 for all 14 common serotypes, based on the serotype-specific IgG geometric mean concentrations (GMCs) as measured by the Pn ECL assay at one month postvaccination (adjusted for baseline IgG level). For most shared serotypes, recipients of V114 generally had numerically higher antibody titers than recipients of PNEUMOVAX™ 23.
	V114 was non-inferior (using a 3-fold margin) to PNEUMOVAX™ 23 for all 14 common serotypes, based on the serotype-specific geometric mean titers (GMTs) as measured by the multiplex opsonophagocytic assay (MOPA-4) at one month postvaccination (adjusted for baseline titer level).
Analysis description	**Safety Analysis** There were no safety hypotheses in this study. Safety and tolerability was assessed by statistical and clinical review of all safety data collected throughout the study. To provide an overall assessment, the incidence rate for each vaccination group, the risk difference between the V114 and PNEUMOVAX™ 23 groups and between the V114 and Prevnar 13™ groups, and the associated 95% CI are provided for broader safety measures such as the proportions of subjects with any injection-site adverse experiences occurring on Days 1 to 14, with any systemic adverse experiences occurring on Days 1 to 14, or with any serious adverse experiences or any vaccine related serious adverse experiences occurring through completion of the subject's participation 6 months postvaccination. Comparisons between the V114 and PNEUMOVAX™ 23 groups were considered primary for this study.
Analysis population and time point description	The All Subjects as Treated (ASaT) population was used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received study vaccine.

Summary	Overall, recipients of V114 reported more injection-site (statistically significant) and systemic adverse events (AEs) relative to recipients of PNEUMOVAX™ 23 or Prevnar 13™. The differences were mainly due to the higher frequencies of solicited systemic AEs (i.e., arthralgia, myalgia) and solicited injection site pain and swelling among recipients of V114 than recipients of PNEUMOVAX™ 23. Among recipients of V114, PNEUMOVAX™ 23, and Prevnar 13™, the proportion of subjects reporting an injection site pain was 60.3%, 51.3%, and 53.0%, respectively while injection site swelling was reported in 20.1%, 10.9%, and 18.3%, respectively. Arthralgia was reported by 17.9%, 11.3%, and 12.6% of recipients of V114, PNEUMOVAX™ 23, and Prevnar 13™, respectively. Myalgia was observed in 29.3%, 26.1%, and 21.7% of recipients of V114, PNEUMOVAX™ 23, and Prevnar 13™, respectively. The majority of these injection site and systemic AEs were transient and mild to moderate in intensity. Serious AEs were reported by 4, 7, and 5 recipients of V114, PNEUMOVAX ™23, and Prevnar 13™, respectively but none of these events were related to the study vaccine.

Analysis of Postvaccination IgG GMCs to the Serotypes in Common with PNEUMOVAX 23
V114 versus PNEUMOVAX 23
(Per-Protocol Population)

Pneumococcal Serotype	V114 (N = 230) Estimated Response† n	V114 (N = 230) Estimated Response† GMC (µg/mL)	PNEUMOVAX 23 (N = 231) Estimated Response† n	PNEUMOVAX 23 (N = 231) Estimated Response† GMC (µg/mL)	Estimated GMC Ratio† [V114 / PNEUMOVAX 23] (95% CI)‡	p-Value†‡
1	210	3.85	207	3.30	1.17 (0.90, 1.52)	<0.001
3	210	1.12	207	0.56	1.99 (1.60, 2.47)	<0.001
4	210	2.05	207	0.96	2.14 (1.67, 2.73)	<0.001
5	210	3.75	207	2.78	1.35 (1.06, 1.72)	<0.001
6B	210	5.39	207	1.93	2.79 (2.11, 3.69)	<0.001
7F	210	4.62	207	3.73	1.24 (0.96, 1.59)	<0.001
9V	210	4.02	207	2.75	1.46 (1.15, 1.86)	<0.001
14	210	8.87	207	8.15	1.09 (0.83, 1.42)	<0.001
18C	210	7.80	207	4.72	1.65 (1.30, 2.10)	<0.001
19A	210	9.44	207	6.74	1.40 (1.10, 1.78)	<0.001
19F	210	3.30	207	4.00	0.82 (0.64, 1.07)	<0.001
22F	210	5.59	207	1.98	2.83 (2.28, 3.51)	<0.001
23F	210	5.18	207	1.83	2.82 (2.14, 3.73)	<0.001
33F	210	11.34	207	8.30	1.37 (1.11, 1.69)	<0.001

†Estimated GMCs, GMC ratio, 95% CI, and p-value are obtained from a cLDA model.
‡A conclusion of non-inferiority is based on the lower bound of the 95% CI on the estimated ratio being>0.5 (one-sided p-value < 0.025).
N = Number of subjects randomized and vaccinated.
n = Number of subjects contributing to the analysis.
GMC = Geometric Mean Concentration.
CI = Confidence interval.

Analysis of Postvaccination OPA GMTs to the Serotypes in Common with PNEUMOVAX 23
V114 versus PNEUMOVAX 23
(Per-Protocol Population)

Pneumococcal Serotype	V114 (N = 230) Estimated Response† n	V114 (N = 230) Estimated Response† GMT (1/dil)	PNEUMOVAX 23 (N = 231) Estimated Response† n	PNEUMOVAX 23 (N = 231) Estimated Response† GMT (1/dil)	Estimated GMT Ratio† [V114 / PNEUMOVAX 23] (95% CI)‡	p-Value†‡
1	210	206.22	207	119.00	1.73 (1.17, 2.57)	<0.001
3	210	597.91	207	304.76	1.96 (1.52, 2.53)	<0.001
4	210	2955.15	207	1071.95	2.76 (1.90, 4.00)	<0.001
5	210	676.39	207	298.63	2.26 (1.55, 3.30)	<0.001
6B	210	6601.38	207	1655.61	3.99 (2.72, 5.85)	<0.001
7F	210	5054.19	207	3726.88	1.36 (0.98, 1.88)	<0.001
9V	210	3060.10	207	1718.25	1.78 (1.25, 2.53)	<0.001
14	210	4211.95	207	3696.99	1.14 (0.82, 1.58)	<0.001
18C	210	4490.22	207	2464.48	1.82 (1.32, 2.51)	<0.001
19A	210	3271.82	207	2645.59	1.24 (0.93, 1.64)	<0.001
19F	210	1178.44	207	1536.25	0.77 (0.55, 1.07)	<0.001
22F	210	7778.98	207	4263.77	1.82 (1.22, 2.74)	<0.001
23F	210	2126.85	207	377.37	5.64 (3.62, 8.77)	<0.001
33F	210	30291.19	207	30112.79	1.01 (0.75, 1.36)	<0.001

†Estimated GMTs, GMT ratio, 95% CI, and p-value are obtained from a cLDA model.
‡A conclusion of non-inferiority is based on the lower bound of the 95% CI on the estimated ratio being>0.33 (one-sided p-value < 0.025).
N = Number of subjects randomized and vaccinated.
n = Number of subjects contributing to the analysis.
GMT = Geometric Mean Titer.
CI = Confidence interval.

Adverse Event Summary
Duration of Study

	V114 n	V114 (%)	PNEUMOVAX 23 n	PNEUMOVAX 23 (%)	Prevnar 13 n	Prevnar 13 (%)	Total n	Total (%)
Subjects in population with follow-up	229		230		230		689	
with one or more adverse events	172	(75.1)	157	(68.3)	151	(65.7)	480	(69.7)
injection-site	151	(65.9)	127	(55.2)	124	(53.9)	402	(58.3)
non-injection-site	114	(49.8)	105	(45.7)	107	(46.5)	326	(47.3)
with no adverse event	57	(24.9)	73	(31.7)	79	(34.3)	209	(30.3)
with vaccine-related† adverse events	161	(70.3)	144	(62.6)	141	(61.3)	446	(64.7)
injection-site	150	(65.5)	127	(55.2)	124	(53.9)	401	(58.2)
non-injection-site	92	(40.2)	80	(34.8)	85	(37.0)	257	(37.3)
with serious adverse events	4	(1.7)	7	(3.0)	5	(2.2)	16	(2.3)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.1)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

CONCLUSIONS:	In healthy adults 50 years of age and older: 1. V114 was non-inferior (using a 2-fold margin) to PNEUMOVAX™ 23 for all 14 common serotypes, based on the serotype-specific IgG GMCs as measured by the Pn ECL assay at one month postvaccination (adjusted for baseline IgG level). 2. V114 was non-inferior (using a 3-fold margin) to PNEUMOVAX™ 23 for all 14 common serotypes, based on the serotype-specific geometric mean titers (GMTs) as measured by the multiplex opsonophagocytic assay (MOPA-4) at one month postvaccination (adjusted for baseline titer level). 3. Both IgG GMCs and OPA GMTs measured following receipt of a single dose of V114 were comparable to those measured following a single dose of either PNEUMOVAX™ 23 or Prevnar 13™ for the common serotypes in adults 50 years of age and older. 4. A single dose of V114 was generally well tolerated.
PUBLICATION(S):	Not Applicable
REPORT DATE:	18-NOV-2014
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