This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. V114 Sterile Suspension Pneumococcal Disease	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Multicenter, Double-Blind Study of the Safety, Tolerability, and Immunogenicity of Pneumococcal Conjugate Vaccine (V114) Compared to Prevnar 13™ in Healthy Infants #003

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information see [16.1.8].

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter: 58 centers in Canada, Finland, Israel, Puerto Rico, Spain, and United States

PUBLICATION(S): None at this time

PRIMARY THERAPY PERIOD: 14-October-2010 to 31-July-2012	**CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Subjects received blinded study vaccine at 2, 4, 6, and 12 to15 months of age.

OBJECTIVE(S): Primary: (1) Demonstrate that 15-valent pneumococcal conjugate vaccine (V114) with aluminum adjuvant or V114 without aluminum adjuvant is non-inferior to 13-valent pneumococcal conjugate vaccine (Prevnar 13™) for the 13 serotypes in common with Prevnar 13™ (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F), based on the proportion of subjects meeting the postdose 3 IgG reference levels. (2) Evaluate the IgG geometric mean concentrations (GMCs) as measured in the pneumococcal electrochemiluminescence (Pn ECL) assay, for recipients of adjuvanted V114, non-adjuvanted V114, and Prevnar 13™ at postdose 3 for each of the 13 pneumococcal serotypes in common with Prevnar 13™. (3) Evaluate the IgG GMCs as measured in the Pn ECL assay, for recipients of adjuvanted V114, non-adjuvanted V114, and Prevnar 13™ at postdose 4 for each of the 13 pneumococcal serotypes in common with Prevnar 13™. (4) Describe and compare the safety profile of the 15-valent pneumococcal conjugate vaccine (V114) with and without aluminum adjuvant to 13-valent pneumococcal conjugate vaccine (Prevnar 13™) after each dose when administered as 4-dose series to healthy infants at 2, 4, 6, and 12 to 15 months of age.

Hypothesis: V114 with aluminum adjuvant is non-inferior to Prevnar 13™, based on the immune responses at postdose 3 to the 13 serotypes in common with Prevnar 13™ (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F): (a) For the 7 serotypes in common with Prevnar™ (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F), the statistical criterion for non-inferiority is that the lower bound of the 95% confidence interval (CI) on the difference (V114 minus Prevnar 13™) in the proportion of subjects meeting the serotype-specific IgG reference level (an antibody concentration measured by the Pn ECL assay corresponding to the World Health Organization Enzyme-linked Immunsorbant Assay (WHO ELISA) value of ≥ 0.35µg/mL) will be greater than -0.15 for each of the 7 serotypes in common with Prevnar™. (b) For the 6 serotypes that are in common with Prevnar 13™ but not with Prevnar™ (serotypes 1, 3, 5, 6A, 7F, 19A), the statistical criterion for non-inferiority is that the lower bound of the 95% confidence interval on the difference (V114 minus Prevnar 13™) in the proportion of subjects meeting the IgG reference level (an antibody concentration of ≥0.59 µg/mL as measured by the Pn ECL assay) will be greater than - 0.15 for each of the 6 serotypes that are in common with Prevnar 13™ but not with Prevnar™. Conditional upon demonstrating non-inferiority of V114 with aluminum adjuvant, the same non-inferiority hypothesis test will be performed comparing V114 without aluminum adjuvant with Prevnar 13™.

STUDY DESIGN: A multicenter, randomized, double-blind (with in-house blinding procedures), worldwide, active control trial to evaluate the safety, tolerability, and immunogenicity of 15-valent pneumococcal conjugate vaccine (V114) compared to Prevnar 13™ in healthy infants. Study vaccines were administered concomitantly with other licensed routine pediatric vaccines administered at 2, 4, 6, and 12 to 15 months of age. Subjects were randomly assigned to 1 of 3 vaccination groups: (1) V114, aluminum adjuvanted, (2) V114, non-adjuvanted, or (3) Prevnar 13™ control arm.

SUBJECT DISPOSITION:

	V114 adjuvanted		V114 non-adjuvanted		PREVNAR 13		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	378		386		378		1,142	
Vaccinated at								
Vaccination 1	378	(100.0)	386	(100.0)	378	(100.0)	1,142	(100.0)
Vaccination 2	355	(93.9)	369	(95.6)	361	(95.5)	1,085	(95.0)
Vaccination 3	347	(91.8)	357	(92.5)	354	(93.7)	1,058	(92.6)
Vaccination 4	329	(87.0)	335	(86.8)	333	(88.1)	997	(87.3)
Study Disposition								
Completed	320	(84.7)	327	(84.7)	326	(86.2)	973	(85.2)
Discontinued	58	(15.3)	59	(15.3)	52	(13.8)	169	(14.8)
Adverse Event	1	(0.3)	1	(0.3)	3	(0.8)	5	(0.4)
Lost To Follow-Up	22	(5.8)	22	(5.7)	16	(4.2)	60	(5.3)
Physician Decision	2	(0.5)	1	(0.3)	0	(0.0)	3	(0.3)
Protocol Violation	1	(0.3)	1	(0.3)	1	(0.3)	3	(0.3)
Study Terminated By Sponsor	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	32	(8.5)	34	(8.8)	31	(8.2)	97	(8.5)

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

There were 1152 subjects randomized into the study.

n=1142 excludes 4 subjects who each received a combination of vaccines and who each had a final disposition of Completed and excludes an additional 6 subjects who were randomized but never vaccinated.

Data Source: [16.4]

DOSAGE/FORMULATION NOS.: A 0.5-mL intramuscular (IM) dose of study vaccine (V114 aluminum adjuvanted, V114 non-adjuvanted, or Prevnar 13™) was administered to healthy infant subjects at 2, 4, 6, and 12 to15 months of age.

Clinical Supplies Used in V114-003-02

Vaccine	Market Lot Number	Dosage Form/Packaging	Bulk Number(s)	Potency (Polysaccharide content per dose)
V114 adjuvanted	NA	0.5-mL single-dose syringe	WL00038620	See footnote[†]
V114 adjuvanted	NA	0.5-mL single-dose syringe	WL00044551	See footnote[†]
V114 nonadjuvanted	NA	0.5-mL single-dose syringe	WL00038471	See footnote[‡]
V114 nonadjuvanted	NA	0.5-mL single-dose syringe	WL00043298	See footnote [‡]
Prevnar 13™	E44520	0.5-mL single-dose syringe	WL00038523	See footnote[§]
Prevnar 13™	E88940	0.5-mL single-dose syringe	WL00041622	See footnote[§]
Prevnar 13™	E70195	0.5-mL single-dose syringe	WL00042347	See footnote[§]
Prevnar 13™	915706	0.5-mL single-dose syringe	WL00042348	See footnote[§]
Prevnar 13™	F32671	0.5-mL single-dose syringe	WL00045497	See footnote[§]
Prevenar 13™	E27415	0.5-mL single-dose syringe	DL00016132	See footnote[§]
Prevenar 13™	E57027	0.5-mL single-dose syringe	DL00017147	See footnote[§]
Prevenar 13™	F14427	0.5-mL single-dose syringe	DL00017323	See footnote [§]

[†]V114 contains 2µg each of 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F and 4µg of 6B; 30µg of CRM_{197} and 125µg of elemental aluminum as aluminum phosphate (MAPA) per 0.5-mL dose.
[‡] V114 nonadjuvanted contains 2µg each of 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F and 4µg of 6B; 30µg of CRM_{197} per 0.5-mL dose.
[§] Prevnar 13™/Prevenar 13™ contains 2.2µg each of 1, 3, 4, 5, 9V, 14, 18C, 19F, 19A and 23F and 4.4µg of 6B; 34µg of CRM_{197} and 125µg of aluminum per 0.5-mL dose.
Note: In Canada, Prevnar 13™ was locally supplied. Lot numbers were not recorded in the database.

Data Source: [Not Applicable]

DIAGNOSIS/INCLUSION CRITERIA: Afebrile healthy infant subjects 6 to 12 weeks (42 to 89 days) old.

EVALUATION CRITERIA: **Immunogenicity:** Serotype-specific IgG concentrations were measured using the Meso-Scale Discovery (MSD) electrochemiluminescence (ECL) assay (MSD is a trademark of Meso Scale Discovery, a division of Meso Scale Diagnostics, LLC., Gaithersburg, MD, U.S.A.) and a multiplex opsonophagocytic assay (OPA) was used to measure functional OPA. The percentage of subjects with postvaccination serotype-specific IgG concentrations corresponding to a level of ≥0.35 µg/mL in the WHO ELISA was evaluated. Other endpoints of interest were the geometric mean concentrations of IgG, the percentage of subjects with opsonophagocytic killing activity as defined by functional antibacterial OPA titer ≥1:8 and the geometric mean OPA titers for the serotypes contained in the V114 vaccine. **Safety:** Adverse experiences (AEs) were collected using a validated vaccination report card (VRC). All adverse experiences were graded for severity. (1) Study subjects were observed for 30 minutes postvaccination for any immediate AEs. (2) Solicited injection-site AEs (redness, swelling, hard lump, and pain/tenderness) and solicited systemic AEs (irritability, drowsiness, appetite lost, and hives or welts) were collected Day 1 to Day 14 after vaccination. (3) Any other systemic or injection-site AEs were collected Day 1 to Day 14 after vaccination. 4) Serious adverse experiences (SAEs) were collected from the time the consent form was signed through completion of the subject's participation in the study at Day 30 after receipt of last dose of study vaccine. 5) Body temperature was measured during Day 1 to Day 7 after vaccination. If fever was suspected, body temperature was also measured during Day 8 to Day 14.

STATISTICAL PLANNING AND ANALYSIS: **Immunogenicity Analyses:** For the primary immunogenicity hypotheses, the primary endpoints were the proportion of subjects with a postdose 3 level of serotype-specific IgG antibody (in the Merck Pn ECL assay) that corresponded to a level of ≥0.35 µg/mL in the internationally accepted WHO ELISA for each of the 7 serotypes in common between V114 and Prevnar™ (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) and the proportion of subjects with a postdose 3 level of serotype-specific IgG of ≥0.59 µg/mL in the Pn ECL assay for each of the 6 serotypes in common between V114 and Prevnar 13™ but not Prevnar™ (serotypes 1, 3, 5, 6A, 7F, 19A). The pre-specified serotype-specific threshold values for the comparisons of the 7 Prevnar™ serotypes were generated from data in a small preliminary bridging experiment. Following the start of the study, a larger, final bridging experiment determined that the serotype-specific threshold value of ≥0.35 µg/mL in the Pn ECL assay could be used for all serotypes. Analyses were provided for both sets of threshold values. Additional primary immunogenicity endpoints were the postdose 3 and postdose 4 IgG GMCs for the 13 serotypes in common with Prevnar 13™. All primary analyses were based on the per-protocol population. For the analysis of the primary hypotheses, non-inferiority (using a 15 percentage point non-inferiority margin) was assessed with a one-sided test (one-sided α=0.025) of the difference (V114 minus Prevnar 13™) in the percentage of subjects who achieved the specified reference level, using the approach of Miettinen and Nurminen. For the primary hypotheses, the tests were executed in an ordered fashion to control multiplicity: The V114 aluminum-adjuvanted arm was tested first, followed by the V114 non-adjuvanted arm (if the adjuvanted arm was non-inferior to Prevnar 13™). Non-inferiority of GMCs was assessed based on the ratio (V114 / Prevnar 13™) of GMCs being >0.5 for each of the 13 serotypes in common with Prevnar 13™. With the proposed sample size of 370 per group, the study had >90% power to declare non-inferiority for the primary hypotheses assuming a 90% evaluability rate. **Safety Analyses:** Safety and tolerability were assessed by clinical review of all relevant parameters including AEs. There were no pre-specified AEs of interest. To provide an overall safety assessment during the 14-day postvaccination follow-up periods (across all vaccinations, and by vaccination), safety measures such as the proportion of subjects with: (1) Any AE, (2) any injection-site AE, (3) any systemic AE, (4) any SAE, and (5) any discontinuation due to an AE were summarized. The risk differences on these overall safety parameters between each V114 formulation and Prevnar 13™ and the corresponding two-sided 95% CI on the risk difference were provided using the asymptotic methods proposed by Miettinen and Nurminen. For AEs specifically prompted for on the VRC the risk differences, the 95% CIs, and the corresponding p-values were provided. For other AEs that were reported in at least 4 subjects within any group, the risk difference and 95% CI were provided. Additionally, the number and percentages were provided for all reported AEs.

RESULTS: Immunogenicity:

Non-Inferiority Analysis of Postdose 3 IgG Antibody Responses to the Serotypes in Common with Prevnar 13™
V114 Adjuvanted versus Prevnar 13™ (Per-Protocol Population)

Pneumococcal Serotype	Reference Level	V114 Adjuvanted Observed Response[†] Percent (m/n)	Prevnar 13 Observed Response[†] Percent (m/n)	Percentage Point Difference [V114 - Prevnar 13] (95% CI)[‡]	p-Value[‡]
Prevnar™ Types[§]					
4	% ≥ 0.40[§] µg/mL	95.3% (286/300)	95.2% (300/315)	0.1 (-3.5, 3.6)	<0.001
	% ≥ 0.35 µg/mL	97.0% (291/300)	96.5% (304/315)	0.5 (-2.5, 3.5)	NA
6B	% ≥ 0.69[§] µg/mL	65.7% (197/300)	76.8% (242/315)	-11.2 (-18.3, -4.0)	0.145
	% ≥ 0.35 µg/mL	73.7% (221/300)	87.6% (276/315)	-14.0 (-20.2, -7.8)	NA
9V	% ≥ 0.66[§] µg/mL	85.3% (256/300)	89.8% (283/315)	-4.5 (-9.9, 0.7)	<0.001
	% ≥ 0.35 µg/mL	95.0% (285/300)	97.5% (307/315)	-2.5 (-5.8, 0.6)	NA
14	% ≥ 0.50[§] µg/mL	97.3% (292/300)	97.1% (306/315)	0.2 (-2.7, 3.0)	<0.001
	% ≥ 0.35 µg/mL	98.7% (296/300)	97.8% (308/315)	0.9 (-1.4, 3.4)	NA
18C	% ≥ 0.71[§] µg/mL	79.3% (238/300)	92.7% (292/315)	-13.4 (-18.9, -8.0)	0.278
	% ≥ 0.35 µg/mL	96.7% (290/300)	97.5% (307/315)	-0.8 (-3.8, 2.0)	NA
19F	% ≥ 0.41[§] µg/mL	90.0% (270/300)	99.0% (312/315)	-9.0 (-13.1, -5.8)	0.003
	% ≥ 0.35 µg/mL	91.3% (274/300)	99.4% (313/315)	-8.0 (-11.8, -5.1)	NA
23F	% ≥ 0.61[§] µg/mL	71.7% (215/300)	81.3% (256/315)	-9.6 (-16.3, -2.9)	0.057
	% ≥ 0.35 µg/mL	87.7% (263/300)	90.8% (286/315)	-3.1 (-8.2, 1.8)	NA
Non-Prevnar™ Types					
1	% ≥ 0.59[§] µg/mL	88.3% (265/300)	93.7% (295/315)	-5.3 (-10.1, -0.8)	<0.001
	% ≥ 0.35 µg/mL	98.0% (294/300)	97.5% (307/315)	0.5 (-2.1, 3.2)	NA
3	% ≥ 0.59[§] µg/mL	78.3% (235/300)	39.4% (124/315)	39.0 (31.6, 45.9)	<0.001
	% ≥ 0.35 µg/mL	93.3% (280/300)	69.2% (218/315)	24.1 (18.3, 30.0)	NA
5	% ≥ 0.59[§] µg/mL	88.0% (264/300)	90.8% (286/315)	-2.8 (-7.8, 2.1)	<0.001
	% ≥ 0.35 µg/mL	95.7% (287/300)	96.2% (303/315)	-0.5 (-3.9, 2.7)	NA
6A	% ≥ 0.59[§] µg/mL	72.3% (217/300)	95.6% (301/315)	-23.2 (-28.9, -17.8)	0.999
	% ≥ 0.35 µg/mL	77.0% (231/300)	96.8% (305/315)	-19.8 (-25.2, -14.9)	NA
7F	% ≥ 0.59[§] µg/mL	97.0% (291/300)	97.8% (308/315)	-0.8 (-3.6, 1.9)	<0.001
	% ≥ 0.35 µg/mL	99.0% (297/300)	99.4% (313/315)	-0.4 (-2.3, 1.4)	NA
19A	% ≥ 0.59[§] µg/mL	66.3% (199/300)	90.8% (286/315)	-24.5 (-30.7, -18.2)	0.999
	% ≥ 0.35 µg/mL	82.7% (248/300)	96.5% (304/315)	-13.8 (-18.9, -9.3)	NA

[†]Proportion of subjects meeting the serotype-specific IgG reference level (measured by the Pn ECL assay).
[‡]Non-inferiority is demonstrated if the lower bound of the 2-sided 95% CI for the percentage point difference is greater than -15, which corresponds to a p-value < 0.025. Point, interval estimates, and p-values were obtained using methods developed by Miettinen and Nurminen.
[§]Serotype-specific reference level based on a preliminary bridging experiment.
n = Number of subjects contributing to the analysis.
m = Number of subjects with the indicated response.
CI = Confidence interval.
NA = Not applicable as primary hypothesis testing was based on the preliminary reference levels.

Data Source: [16.4]

Analysis of Postdose 3 IgG Antibody Responses to the Serotypes in Common with Prevnar 13™ V114 Non-Adjuvanted versus Prevnar 13™ (Per-Protocol Population)

Pneumococcal Serotype	Reference Level	V114 Non-Adjuvanted Observed Response[†] Percent (m/n)	Prevnar 13 Observed Response[†] Percent (m/n)	Percentage Point Difference [V114 - Prevnar 13] (95% CI)[‡]
Prevnar™ Types[§]				
4	% ≥ 0.40[§] µg/mL	92.7% (292/315)	95.2% (300/315)	-2.5 (-6.5, 1.2)
	% ≥ 0.35 µg/mL	94.0% (296/315)	96.5% (304/315)	-2.5 (-6.1, 0.8)
6B	% ≥ 0.69[§] µg/mL	56.5% (178/315)	76.8% (242/315)	-20.3 (-27.4, -13.0)
	% ≥ 0.35 µg/mL	65.4% (206/315)	87.6% (276/315)	-22.2 (-28.6, -15.8)
9V	% ≥ 0.66[§] µg/mL	77.5% (244/315)	89.8% (283/315)	-12.4 (-18.2, -6.7)
	% ≥ 0.35 µg/mL	92.4% (291/315)	97.5% (307/315)	-5.1 (-8.8, -1.7)
14	% ≥ 0.50[§] µg/mL	96.5% (304/315)	97.1% (306/315)	-0.6 (-3.6, 2.3)
	% ≥ 0.35 µg/mL	98.4% (310/315)	97.8% (308/315)	0.6 (-1.7, 3.1)
18C	% ≥ 0.71[§] µg/mL	70.8% (223/315)	92.7% (292/315)	-21.9 (-27.8, -16.2)
	% ≥ 0.35 µg/mL	89.8% (283/315)	97.5% (307/315)	-7.6 (-11.7, -4.0)
19F	% ≥ 0.41[§] µg/mL	88.6% (279/315)	99.0% (312/315)	-10.5 (-14.6, -7.1)
	% ≥ 0.35 µg/mL	91.1% (287/315)	99.4% (313/315)	-8.3 (-12.0, -5.3)
23F	% ≥ 0.61[§] µg/mL	64.4% (203/315)	81.3% (256/315)	-16.8 (-23.6, -10.0)
	% ≥ 0.35 µg/mL	81.6% (257/315)	90.8% (286/315)	-9.2 (-14.7, -3.9)
Non-Prevnar™ Types				
1	% ≥ 0.59[§] µg/mL	85.7% (270/315)	93.7% (295/315)	-7.9 (-12.8, -3.3)
	% ≥ 0.35 µg/mL	96.2% (303/315)	97.5% (307/315)	-1.3 (-4.3, 1.6)
3	% ≥ 0.59[§] µg/mL	73.3% (231/315)	39.4% (124/315)	34.0 (26.5, 41.0)
	% ≥ 0.35 µg/mL	89.8% (283/315)	69.2% (218/315)	20.6 (14.5, 26.8)
5	% ≥ 0.59[§] µg/mL	84.8% (267/315)	90.8% (286/315)	-6.0 (-11.3, -0.9)
	% ≥ 0.35 µg/mL	92.4% (291/315)	96.2% (303/315)	-3.8 (-7.7, -0.2)
6A	% ≥ 0.59[§] µg/mL	68.3% (215/315)	95.6% (301/315)	-27.3 (-33.0, -21.8)
	% ≥ 0.35 µg/mL	78.4% (247/315)	96.8% (305/315)	-18.4 (-23.6, -13.6)
7F	% ≥ 0.59[§] µg/mL	96.8% (305/315)	97.8% (308/315)	-1.0 (-3.8, 1.7)
	% ≥ 0.35 µg/mL	99.4% (313/315)	99.4% (313/315)	0.0 (-1.7, 1.7)
19A	% ≥ 0.59[§] µg/mL	71.7% (226/315)	90.8% (286/315)	-19.0 (-25.0, -13.2)
	% ≥ 0.35 µg/mL	84.4% (266/315)	96.5% (304/315)	-12.1 (-16.8, -7.7)

[†]Proportion of subjects meeting the serotype-specific IgG reference level (measured by the Pn ECL assay).

[‡]Point, interval estimates were obtained using methods developed by Miettinen and Nurminen.

[§]Serotype-specific reference level based on a preliminary bridging experiment.

n = Number of subjects contributing to the analysis.

m = Number of subjects with the indicated response.

CI = Confidence interval.

Data Source: [16.4]

Non-Inferiority Analysis of Postdose 3 IgG GMCs to the Serotypes in Common with Prevnar 13™ (Per-Protocol Population)

Pneumococcal Serotype	V114 Formulation	V114 Observed Response		Prevnar 13 Observed Response		Fold Difference [V114/Prevnar 13]
		n	GMC (µg/mL)	n	GMC (µg/mL)	(95% CI)[†]
Prevnar™ Types						
4	Adjuvanted	300	1.28	315	1.32	0.97 (0.86, 1.09)
	Non-Adjuvanted	315	1.26			0.95 (0.85, 1.07)
6B	Adjuvanted	300	0.95	315	1.47	0.65 (0.51, 0.82)
	Non-Adjuvanted	315	0.69			0.47 (0.37, 0.60)
9V	Adjuvanted	300	1.49	315	1.79	0.83 (0.73, 0.95)
	Non-Adjuvanted	315	1.29			0.72 (0.62, 0.83)
14	Adjuvanted	300	4.17	315	5.62	0.74 (0.64, 0.87)
	Non-Adjuvanted	315	3.84			0.68 (0.58, 0.80)
18C	Adjuvanted	300	1.27	315	1.99	0.64 (0.56, 0.73)
	Non-Adjuvanted	315	1.08			0.54 (0.47, 0.63)
19F	Adjuvanted	300	1.50	315	2.54	0.59 (0.51, 0.68)
	Non-Adjuvanted	315	1.71			0.67 (0.58, 0.78)
23F	Adjuvanted	300	1.05	315	1.41	0.75 (0.64, 0.88)
	Non-Adjuvanted	315	0.79			0.56 (0.47, 0.66)
Non-Prevnar™ Types						
1	Adjuvanted	300	1.34	315	1.84	0.73 (0.65, 0.82)
	Non-Adjuvanted	315	1.38			0.75 (0.66, 0.85)
3	Adjuvanted	300	0.95	315	0.50	1.89 (1.69, 2.12)
	Non-Adjuvanted	315	0.88			1.75 (1.56, 1.98)
5	Adjuvanted	300	1.61	315	1.83	0.88 (0.76, 1.01)
	Non-Adjuvanted	315	1.53			0.84 (0.72, 0.97)
6A	Adjuvanted	300	0.93	315	2.91	0.32 (0.27, 0.38)
	Non-Adjuvanted	315	0.93			0.32 (0.26, 0.38)
7F	Adjuvanted	300	2.63	315	3.67	0.72 (0.64, 0.80)
	Non-Adjuvanted	315	2.66			0.73 (0.65, 0.81)
19A	Adjuvanted	300	0.90	315	2.05	0.44 (0.38, 0.51)
	Non-Adjuvanted	315	0.94			0.46 (0.39, 0.53)

[†]Non-inferiority is demonstrated if the lower bound of the 2-sided 95% CI for the fold difference is greater than 0.5.

n = Number of subjects contributing to the analysis.

GMC = Geometric Mean Concentration.

CI = Confidence interval.

Data Source: [16.4]

Non-Inferiority Analysis of Postdose 4 IgG GMCs to the Serotypes in Common with Prevnar 13™ (Per-Protocol Population)

Pneumococcal Serotype	V114 Formulation	V114 Observed Response		Prevenar 13 Observed Response		Fold Difference [V114/Prevnar 13]
		n	GMC (µg/mL)	n	GMC (µg/mL)	(95% CI)[†]
Prevnar™ Types						
4	Adjuvanted	274	1.46	281	1.68	0.87 (0.74, 1.02)
	Non-Adjuvanted	298	1.40			0.83 (0.72, 0.95)
6B	Adjuvanted	275	5.24	281	5.51	0.95 (0.81, 1.12)
	Non-Adjuvanted	298	3.98			0.72 (0.61, 0.86)
9V	Adjuvanted	273	2.82	281	3.37	0.84 (0.72, 0.97)
	Non-Adjuvanted	298	2.50			0.74 (0.65, 0.85)
14	Adjuvanted	275	6.05	282	7.57	0.80 (0.68, 0.94)
	Non-Adjuvanted	298	5.55			0.73 (0.63, 0.85)
18C	Adjuvanted	275	2.14	281	3.37	0.64 (0.55, 0.73)
	Non-Adjuvanted	298	1.68			0.50 (0.44, 0.57)
19F	Adjuvanted	275	5.56	282	4.51	1.23 (1.06, 1.43)
	Non-Adjuvanted	298	6.35			1.41 (1.21, 1.64)
23F	Adjuvanted	275	1.99	280	3.14	0.63 (0.53, 0.75)
	Non-Adjuvanted	298	1.61			0.51 (0.43, 0.60)
Non-Prevnar™ Types						
1	Adjuvanted	275	1.91	283	2.18	0.88 (0.77, 1.00)
	Non-Adjuvanted	298	1.81			0.83 (0.73, 0.95)
3	Adjuvanted	272	1.26	282	0.69	1.83 (1.61, 2.09)
	Non-Adjuvanted	296	1.12			1.63 (1.45, 1.84)
5	Adjuvanted	275	1.93	282	2.53	0.76 (0.66, 0.88)
	Non-Adjuvanted	298	1.79			0.71 (0.62, 0.82)
6A	Adjuvanted	274	3.78	279	6.55	0.58 (0.49, 0.68)
	Non-Adjuvanted	297	3.17			0.48 (0.41, 0.57)
7F	Adjuvanted	274	4.18	282	5.73	0.73 (0.64, 0.84)
	Non-Adjuvanted	298	3.43			0.60 (0.53, 0.68)
19A	Adjuvanted	275	3.04	281	6.14	0.50 (0.43, 0.57)
	Non-Adjuvanted	298	3.42			0.56 (0.48, 0.65)

[†]Non-inferiority is demonstrated if the lower bound of the 2-sided 95% CI for the fold difference is greater than 0.5.
n = Number of subjects contributing to the analysis.
GMC = Geometric Mean Concentration.
CI = Confidence interval.

Data Source: [16.4]

Safety:

Adverse Event Summary Following Any Vaccination

	V114 adjuvanted		V114 non-adjuvanted		PREVNAR 13		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	368		382		376		1,126	
with one or more adverse events	349	(94.8)	359	(94.0)	354	(94.1)	1,062	(94.3)
injection-site	307	(83.4)	302	(79.1)	304	(80.9)	913	(81.1)
non-injection-site	342	(92.9)	352	(92.1)	347	(92.3)	1,041	(92.5)
with no adverse event	19	(5.2)	23	(6.0)	22	(5.9)	64	(5.7)
with vaccine-related† adverse events	336	(91.3)	342	(89.5)	342	(91.0)	1,020	(90.6)
injection-site	307	(83.4)	302	(79.1)	304	(80.9)	913	(81.1)
non-injection-site	306	(83.2)	308	(80.6)	311	(82.7)	925	(82.1)
with serious adverse events	25	(6.8)	27	(7.1)	29	(7.7)	81	(7.2)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	1	(0.3)	1	(0.3)	2	(0.5)	4	(0.4)
discontinued‡ due to an adverse event	1	(0.3)	1	(0.3)	3	(0.8)	5	(0.4)
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	1	(0.3)	1	(0.3)	2	(0.5)	4	(0.4)
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.

Note: Subjects can appear in more than one category.

Data Source: [16.4]

CONCLUSIONS: Immunogenicity: Both V114 adjuvanted and V114 non-adjuvanted induce serotype-specific IgG and OPA to all 15 serotypes included in the vaccine. Overall, recipients of V114 adjuvanted had numerically higher IgG GMCs and OPA GMTs than recipients of V114 non-adjuvanted for the majority of serotypes. In comparison to Prevnar 13™, V114 adjuvanted is non-inferior for 10 shared serotypes but is inferior on 3 serotypes, based on the proportion of subjects achieving the WHO accepted threshold value of ≥0.35µg/mL and GMC ratios at both postdose 3 and postdose 4. Both formulations of V114 induce higher antibody levels than does Prevnar 13™ to serotypes 22F and 33F, the 2 serotypes included in V114 but not contained in Prevnar 13™. **Safety:** Both V114 adjuvanted and V114 non-adjuvanted display acceptable safety profiles comparable to that observed in recipients of Prevnar 13™