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A Phase II Trial of Safety, Tolerability and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine, Compared With 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants

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Background: Pneumococcal disease remains a public health priority worldwide. This phase 2 study (V114-008; NCT02987972; EudraCT 2016-001117-25) compared safety and immunogenicity of 2 clinical lots of V114 (investigational 15-valent pneumococcal vaccine: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F*, 23F, 33F*) to 13-valent pneumococcal conjugate vaccine (PCV13) in healthy infants (*serotypes unique to V114).

Methods: Healthy infants 6–12 weeks old were randomized to receive a 4-dose regimen of V114 Lot 1, V114 Lot 2 or PCV13 at 2, 4, 6 and 12–15 months old. Adverse events were evaluated after each dose. Primary immunogenicity endpoint was to demonstrate noninferiority of V114 Lot 1 and V114 Lot 2 relative to PCV13 based on proportion of infants achieving serotype-specific IgG concentration ≥0.35 µg/mL for 13 serotypes shared with PCV13 at 1 month postdose 3 (PD3). Serotype-specific IgG geometric mean concentrations (GMCs) for all 15 V114 serotypes were measured at PD3, predose 4 and 1 month postdose 4 (PD4).

Results: Overall, 1044 of 1051 randomized infants received ≥1 dose of vaccine (V114 Lot 1 [n = 350], V114 Lot 2 [n = 347] or PCV13 [n = 347]). Adverse events were generally comparable across groups. At PD3, both V114 lots met noninferiority criteria for all 13 serotypes shared with PCV13. IgG GMCs were comparable among V114 and PCV13 recipients at PD3 and PD4. Serotype 3 responses were higher following receipt of V114 than PCV13. Both V114 lots induced higher GMCs than PCV13 to the 2 unique V114 serotypes.

Conclusions: Immunogenicity of both V114 lots was noninferior to PCV13 for all 13 shared serotypes between the 2 vaccines and displayed comparable safety and tolerability profiles to PCV13.

Key Words: pneumococcal conjugate vaccine, safety, immunogenicity

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Pneumococcal infection is associated with high morbidity and mortality in adults ≥65 years of age and young children <5 years of age. There is a higher case fatality ratio due to invasive pneumococcal disease (IPD) (meningitis, sepsis/bacteremia without focus, bacteremic pneumonia) compared with non-IPD (sinusitis, otitis media, nonbacteremic pneumonia).[1–3] In infants, IPD occurs as maternal antibodies wane, and bacteremia without focus is the most common manifestation. In the United States, *Streptoococcus pneumoniae* is a common cause of acute otitis media and leading cause of bacterial meningitis in children younger than 5 years of age.[3] With the introduction of pneumococcal vaccines, the mortality estimate has decreased from over 1 million deaths in children <5 years of age in 2000 to approximately 300,000 in children <5 years of age in 2015, with the greatest burden in developing countries.[4–7]

Several pneumococcal conjugate vaccines (PCVs) have been developed to address the burden of pneumococcal disease in children. A 7-valent PCV containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (PCV7: Prevnar; Pfizer, Philadelphia, PA) was first introduced in 2000 followed later by 10-valent PCV (PCV10: Synflorix; GlaxoSmithKline, Rixensart, Belgium) and 13-valent PCV (PCV13: Prevnar 13; Pfizer, Philadelphia, PA).[8,9] Widespread use of PCVs has been associated with significant reduction in hospitalizations for pneumonia, as well as nasopharyngeal carriage and IPD caused by the serotypes included in these vaccines, both in vaccinated children and unvaccinated individuals from other age groups (herd protection).[9–18] This impact of PCV13 on IPD caused by serotype 3 has not been observed; in many countries, the incidence of serotype 3 IPD has remained relatively stable.[19,20] This in part could be due to the higher estimated IgG concentration needed for protection against IPD caused by serotype 3 than levels measured following vaccination of infants with PCV13.[21]

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In children, IPD due to pneumococcal serotypes not contained in currently available PCVs remains a concern. With the introduction of PCV7 and PCV13, serotype replacement and increased prevalence of IPD due to serotypes not included in the licensed PCV has been observed.[22] IPD caused by serotypes 3, 6A, 7F and 19A increased following widespread use of PCV7 in the United States and many countries worldwide.[4,9] For example, the proportion of IPD caused by serotype 19A in US children was approximately 3% before the introduction of PCV7; however, after introduction of PCV7, which does not include serotype 19A, the prevalence increased to approximately 47%.[4,23,24] A similar increase was observed in other countries, including Australia, Canada, France, Israel, New Zealand and the United Kingdom, where serotype 19A accounted for 4%–10% of IPD but increased to 15%–45% after introduction of PCV7.[5,9,22] Following the introduction of PCV13, a similar serotype replacement has been observed in IPD caused by serotypes 22F and 33F. Although only contributing for 1.2% of all IPD cases in US children under 5 years of age in 1998–1999, IPD caused by these 2 serotypes increased between 2010 and 2014 to approximately 11%–17% and 10%–12% for 22F and 33F, respectively.[4,22,25,26] This phenomenon of serotype replacement substantiates the need for the development of more broadly based pneumococcal conjugate vaccines.[25,27–29]

V114 is an investigational 15-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein; Merck & Co., Inc.) that contains the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) plus serotypes 22F and 33F.[30] Early studies of V114 tested hypotheses related to pneumococcal polysaccharide concentrations, adjuvant amount and conjugation process parameters as it relates to immunogenicity, which led to an improved formulation that demonstrated improved antibody responses in infants.[31,32] In consideration of the findings from the small phase 1/2 study evaluating the new vaccine formulation, and to demonstrate reproducibility in a larger number of infants, this phase 2 study was conducted to compare the safety, tolerability and immunogenicity of V114 compared with PCV13 in healthy infants (V114-008; NCT02987972; EudraCT 2016-001117-25).

METHODS

Study Design

This randomized, multisite, double-blind phase 2 study compared the safety, tolerability and immunogenicity profiles of 2 different lots of V114 compared with PCV13 in healthy infants 6–12 weeks of age. It was conducted from March 21, 2017, through July 9, 2019, at 47 sites (Finland [8], Spain [2], Israel [3], Denmark [2], Canada [3] and the United States [29]). The study was designed to enroll approximately 1050 participants randomized in a 1:1:1 ratio to either V114 Lot 1, V114 Lot 2 or PCV13 vaccination groups. Two different lots of V114 were included in the study to ensure manufacturing consistency and support for further clinical development. A 0.5-mL dose of study vaccine was administered intramuscularly to healthy infants at approximately 2, 4, 6 and 12–15 months of age. Study vaccines were administered concomitantly with other routine pediatric vaccines per local guidelines.

Blood samples were collected at 3 time points: (1) approximately 1 month following the third study vaccination (postdose 3 [PD3]), (2) immediately before administration of the fourth study vaccination (predose 4) and (3) approximately 1 month following the fourth study vaccination (PD4). Sera were used to measure vaccine-induced pneumococcal-specific immune responses (IgG and opsonophagocytic killing activity [OPA]). These serum samples were assayed using the pneumococcal electrochemiluminescence assay, which was developed by Merck & Co., Inc., for the measurement of serotype-specific pneumococcal capsular polysaccharide IgG antibodies.[33,34] Serum samples were also assayed using a microcolony multiplex opsonophagocytic assay (MOPA), developed by Merck & Co., Inc.[35]

To ensure that infants achieved adequate protection against pneumococcal disease caused by PCV13 serotypes before reaching 12 months of age, a rescue criterion was implemented after measurement of immune responses following the primary infant series. The use of the ≥0.35-µg/mL threshold value has been recommended as an acceptable threshold value for evaluating the clinical performance of pneumococcal conjugate vaccines.[36,37] As soon as serologic results were available, any study subject who had serotype-specific IgG geometric mean concentration (GMC) <0.35 µg/mL for serotype 19A individually or ≥4 serotypes in common between V114 and PCV13 was discontinued from the study for lack of efficacy and given 1 dose of licensed PCV13, typically by 10–11 months of age (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E54).

Injection-site and systemic adverse events (AEs) were collected for 14 days postvaccination on a validated hand-held electronic Vaccine Report Card. Solicited injection-site AEs included redness, swelling, hard lump and pain/tenderness, and solicited systemic AEs included irritability, drowsiness, hives/welts and loss of appetite. Body temperature was measured days 1 through 7 postvaccination. Serious AEs were collected from the time the consent form was signed through the duration of participation in the study at 1-month PD4.

Statistical Methods

Serotype-specific antibody responses were assessed PD3 to test the hypothesis that V114 (either Lot 1 or Lot 2) was noninferior to PCV13 for the 13 shared serotypes based on the proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL. The statistical criterion for noninferiority corresponds to the lower bound of the adjusted 95% confidence interval (CI) of the proportion difference (V114 − PCV13) being greater than −0.15 for each of the 13 shared serotypes. The Miettinen and Nurminen approach was used for the comparison.[38] Additionally, at PD3, within-group GMCs and GMC ratios (V114/PCV13) along with 2-sided 95% CIs were computed for each of the 2 V114 lots relative to PCV13 for all 15 serotypes included in V114. All statistical tests were conducted at the $\alpha = 0.05$ (2-sided) level.

The secondary study objective was to evaluate the serotype-specific IgG GMCs of V114 Lot 1, V114 Lot 2 and PCV13, and the IgG GMC ratios between each of the 2 V114 lots and PCV13 for all 15 serotypes included in V114 at predose 4 and 1-month PD4. Additional study objectives were to: evaluate the serotype-specific IgG response rates of V114 Lot 1, V114 Lot 2 and PCV13, and the differences in IgG response rates between each of the 2 V114 lots and PCV13 for the 2 serotypes unique to V114 (22F and 33F) at 1-month PD3 and all 15 serotypes included in V114 at predose 4 and 1-month PD4; and to describe the proportions of subjects with OPA titer ≥lower limit of quantification and OPA geometric mean titers (GMTs) as measured by MOPA in subjects receiving V114 Lot 1, V114 Lot 2 and PCV13 for all 15 serotypes included in V114 at 1-month PD3, predose 4 and 1-month PD4.

The per-protocol (PP) population served as the primary population for the analysis of immunogenicity data in this study. The PP population consisted of those subjects who received the scheduled doses of study vaccine and had valid serology results available for each specific dose. The OPA analysis was conducted on a subset of the PP population which included approximately 50% of subjects enrolled from US sites with sufficient sera available to perform both the pneumococcal electrochemiluminescence and the MOPA testing on all 15 serotypes in V114 using a validated assay with serotype-specific lower limit of quantification values. The all-subjects-as-treated

population was used for the analysis of safety data in this trial. The all-subjects-as-treated population consists of all randomized subjects who received at least 1 dose of study vaccine.

RESULTS

Study Population

Of the 1051 participants randomized, 1044 participants received at least 1 dose of study vaccine, 927 (88.2%) completed the 4-dose vaccine regimen and 921 completed the final study visit (87.6%) (Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E54). Overall, 130 (12.4%) participants discontinued the study. The number of participants who discontinued the study was generally comparable across vaccination groups. The 2 most common reasons for discontinuation were withdrawal by parent/guardian and meeting rescue criteria due to a lack of immune response at PD3.

The intervention groups were generally balanced for baseline characteristics such as age, gender, race and ethnicity (Table, Supplemental Digital Content 3, http://links.lww.com/INF/E54). The reported medical history conditions, prior medications and concomitant medications were balanced across vaccination groups.

Safety

Vaccination with V114 Lot 1, V114 Lot 2 or PCV13 was generally well tolerated. Most participants (>96%) experienced ≥1 AEs after any vaccination, and the overall proportions of injection-site or systemic AEs were generally comparable across vaccination groups (Table 1); summaries of AEs following each dose are shown in Tables, Supplemental Digital Content 4, http://links.lww.com/INF/E54-7 and http://links.lww.com/INF/E54.

Most participants (75%) experienced ≥1 injection-site AEs following any vaccination through the end of study. Injection site AEs were more frequent PD1 and PD2 in the V114 groups compared with the PCV13 group, although the frequency of injection site AEs, including injection site pain, was comparable across all vaccination groups PD3 and PD4 (Tables, Supplemental Digital Content 4, http://links.lww.com/INF/E54-7; and http://links.lww.com/INF/E54). The majority of solicited injection site reactions across the 3 treatment groups were mild to moderate in intensity (Fig. 1).

The majority of vaccine-related systemic AEs were those solicited in the trial, including irritability, drowsiness (somnolence) and appetite loss (decreased appetite) (Table, Supplemental Digital Content 8, http://links.lww.com/INF/E54). Other vaccine-related systemic AEs reported with a frequency of ≥5% included pyrexia and diarrhea. The overall proportions of participants with vaccine-related systemic AEs were comparable across vaccination groups. Similar trends were observed following each vaccination (Tables, Supplemental Digital Content 4, http://links.lww.com/INF/E54-7; and http://links.lww.com/INF/E54).

Elevated temperatures were reported at comparable frequencies across the 3 treatment groups following any vaccination, with comparable frequencies reporting an elevated body temperature ≥39.0°C (≥102.2°F) through 7 days following vaccination.

The incidence of participants who experienced serious adverse events (SAEs) was low (5%) and comparable across vaccination groups. During the study, 1 participant died (sudden infant death of unknown cause; 19 days PD1, V114 Lot 1), and the event was considered not related to study vaccine by the investigator. Two participants experienced vaccine-related SAEs; 1 participant experienced febrile convulsion 2 days PD1 (V114 Lot 2) and discontinued study vaccine. Another participant experienced purpura, categorized as mild, 2 days PD4 (V114 Lot 2).

Immunogenicity

Antibody Responses 1-Month PD3

For both lots of V114, noninferiority was demonstrated for each of the 13 shared serotypes compared with PCV13 as assessed by IgG response rates at 1-month PD3 (Fig. 2). The lower bound of the 2-sided 95% CI for the between-treatment difference in response rates was >−15% points for all 13 shared serotypes. Response rates at 1-month PD3 were generally comparable across the treatment groups for the 13 common serotypes, with some serotype-specific variability noted. In V114 (either Lot 1 or Lot 2), response rates ranged from 92.3% to 100% for serotype 6B and 19F, respectively, while in PCV13 response rates ranged from 71.7% to 99% for serotype 3 and 7F, respectively. Serotype-specific IgG GMCs at 1-month PD3 were generally comparable between V114 Lot 1, V114 Lot 2 and PCV13 for the 13 shared serotypes (Fig. 3). Serotype-specific concentrations did vary for the serotypes in common, with notably higher and lower concentrations observed

TABLE 1. Adverse Event Summary—Post Any Vaccination Through End of Study, All-participants-as-treated Population

	V114 Lot 1		V114 Lot 2		PCV13	
	N	%	n	%	n	%
Subjects in population	350		347		347	
With ≥1 AEs	335	(95.7)	339	(97.7)	332	(95.7)
With vaccine-related AEs	325	(92.9)	330	(95.1)	326	(93.9)
Injection site	268	(76.6)	268	(77.2)	245	(70.6)
Systemic	308	(88.0)	320	(92.2)	316	(91.1)
With serious AEs	18	(5.1)	19	(5.5)	15	(4.3)
With serious vaccine-related AEs*	0	0.0	2	(0.6)	0	0.0
Who died	1	(0.3)	0	0.0	0	0.0
Discontinued due to AE	1	(0.3)	1	(0.3)	0	0.0
Discontinued due to vaccine-related AE	1	(0.3)	1	(0.3)	0	0.0
Discontinued due to serious AE	0	0.0	1	(0.3)	0	0.0
Discontinued due to serious vaccine-related AE*	0	0.0	1	(0.3)	0	0.0
With temperature data†	349		347		344	
≥100.4°F (38.0°C) and <102.2°F (39.0°C)	208	59.6	190	54.8	199	57.8
≥102.2°F (39.0°C)	30	8.6	38	10.9	37	10.8

*Determined by the investigator to be related to the vaccine.

†Temperature solicited days 1–7 after each vaccination. Multiple occurrences of maximum temperature counted only once. Nonrectal temperatures converted to rectal equivalent.

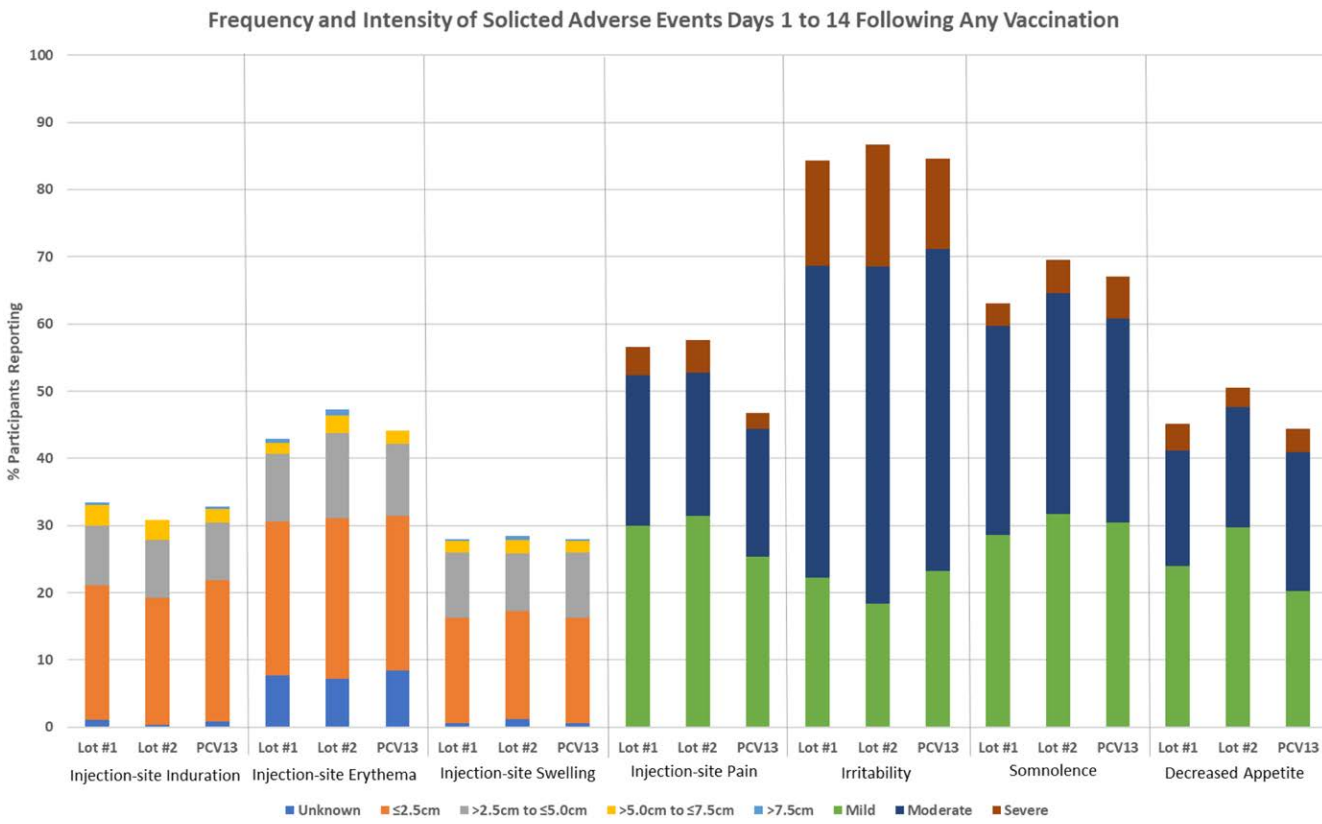

FIGURE 1. Frequency and intensity of injection-site and systemic adverse events days 1–14 following any vaccination.

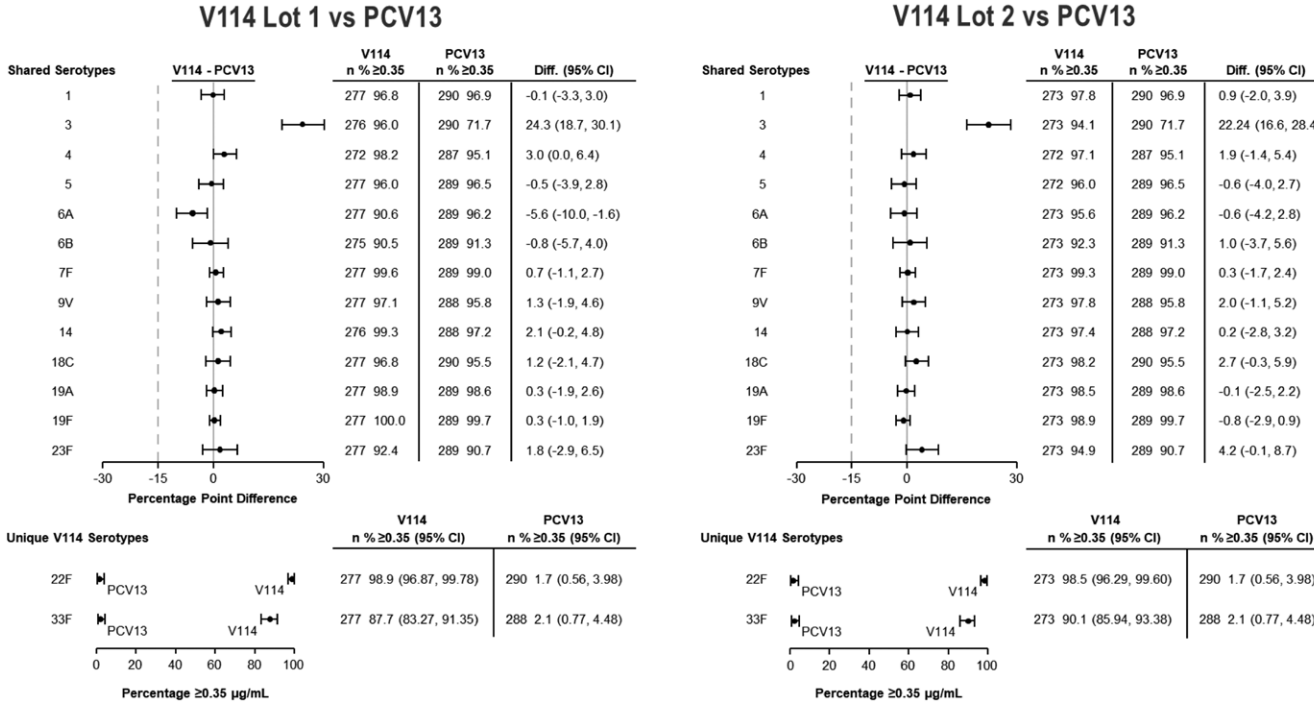

FIGURE 2. IgG antibody response rates 1-month PD3 V114 versus PCV13.

for serotype 14 and serotype 3, respectively, irrespective of treatment group. Although numerical differences were observed for some serotypes between V114 (either Lot 1 or Lot 2) and PCV13, no formal hypotheses were tested.

Response rates and IgG GMCs at 1-month PD3 were higher for the 2 serotypes unique to V114 (22F and 33F) for both lots of V114 when compared with PCV13 (Figs. 2 and 3).

Antibody Responses Predose 4 and 1-Month PD4

In all treatment groups, response rates generally decreased predose 4 compared with PD3 (Figure, Supplemental Digital Content 9, http://links.lww.com/INF/E54), and response rates increased 1-month PD4 for all serotypes across the treatment groups (Figure, Supplemental Digital Content 10, http://links.lww.com/INF/E54), indicating the establishment of a memory response. Interestingly, higher response rates, IgG GMCs, OPA response rates and OPA GMTs were observed at all time points for serotype 3 in recipients of both lots of V114 compared with PCV13. For the 13 shared serotypes, IgG GMCs predose 4 and 1-month PD4 varied by serotype but were generally comparable across the V114 Lot 1, V114 Lot 2 and PCV13 groups (Figure, Supplemental Digital Content 11, http://links.lww.com/INF/E54). Serotype 22F and 33F response rates and IgG GMCs predose 4 and 1-month PD4 were higher in the V114 Lot 1 and V114 Lot 2 groups compared with the PCV13 group (Figure, Supplemental Digital Content 12, http://links.lww.com/INF/E54).

Reverse cumulative distribution curves show that IgG concentrations at 1-month PD3 and PD4 were generally comparable across the 3 vaccination groups for the 13 shared serotypes between V114 and PCV13 (Figures, Supplemental Digital Content 13, http://links.lww.com/INF/E54-27; http://links.lww.com/INF/E54).

OPA was measured in a subset of approximately 100 infants enrolled in the United States who had sufficient blood volume to measure both IgG and OPA. In general, the trends in serotype-specific OPA response rates and GMTs observed at 1-month PD3 (Table 2), predose 4 and 1-month PD4 were comparable to the trends observed in IgG antibody responses at each respective time point.

There were 33 (3.5%) participants who met the protocol-specified rescue criterion for lack of immune response, and these participants were offered vaccination with licensed PCV13 after discontinuation from the study. The proportion of participants meeting rescue criterion was balanced across vaccination groups (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E54).

DISCUSSION

This study demonstrated that the immune responses of both V114 Lot 1 and V114 Lot 2 were noninferior to PCV13 for all 13 shared serotypes. Higher immunogenicity for serotype 3 was observed for both lots of V114 compared with PCV13. This is noteworthy given the conflicting evidence regarding effectiveness of PCV13 against serotype 3 IPD and the lack of a well-accepted antibody threshold required for protection.[21,39–41] The overall significance of this observation for serotype 3 is unclear, as this observation is limited to immunogenicity. Lower IgG GMC for serotype 6A was observed for both lots of V114 compared with PCV13;

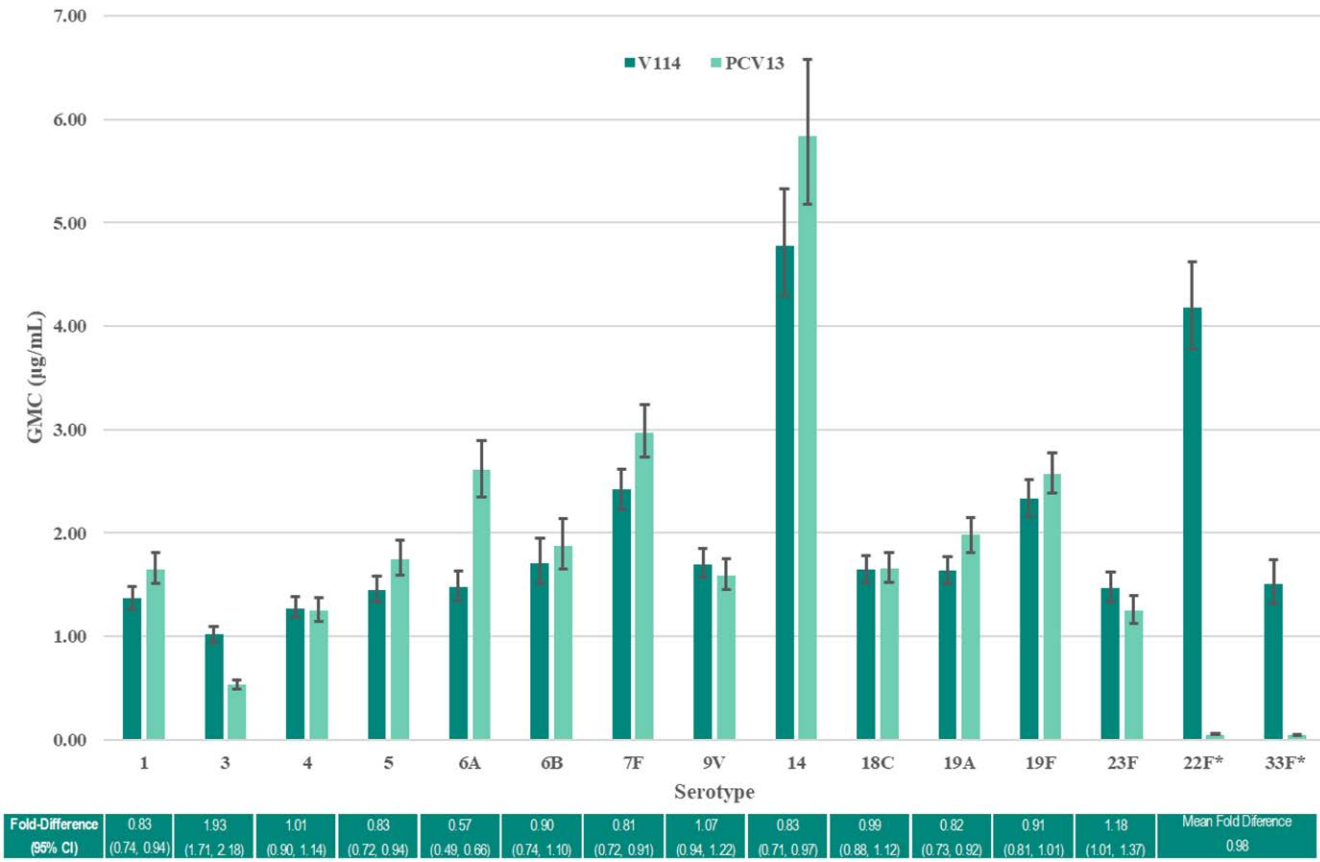

FIGURE 3. IgG GMC antibody responses 1-month PD3 V114 Lot 2 versus PCV13.

TABLE 2. Summary of OPA Antibody Responses PD3 V114 Lot 1, V114 Lot 2 PCV13 (Per-Protocol Population)

		V114 Lot 1 (N = 128)			V114 Lot 2 (N = 136)			PCV13 (N = 128)		
Serotype	Endpoint	N	Observed Response	95% CI	N	Observed Response	95% CI	N	Observed Response	95% CI
Shared serotypes										
1	% ≥ 1:9	104	81%	(72–88)	112	80%	(71–87)	104	76%	(67–84)
	OPA GMT	104	31	(24–40)	112	28	(22–36)	104	28	(22–37)
3	% ≥ 1:19	105	100%	(97–100)	111	99%	(95–100)	103	95%	(89–98)
	OPA GMT	105	160	(142–179)	111	144	(127–165)	103	129	(108–155)
4	% ≥ 1:34	102	100%	(96–100)	110	98%	(94–100)	95	98%	(93–100)
	OPA GMT	102	970	(812–1158)	110	904	(758–1077)	95	1043	(835–1303)
5	% ≥ 1:27	105	97%	(92–99)	114	96%	(90–99)	106	97%	(92–99)
	OPA GMT	105	419	(341–514)	114	392	(319–483)	106	402	(323–502)
6A	% ≥ 1:232	95	98%	(93–100)	101	99%	(95–100)	88	100%	(96–100)
	OPA GMT	95	2144	(1799–2556)	101	1948	(1659–2288)	88	2593	(2115–3179)
6B	% ≥ 1:40	101	100%	(96–100)	108	97%	(92–99)	98	100%	(96–100)
	OPA GMT	101	1261	(1049–1516)	108	1223	(998–1498)	98	1135	(942–1367)
7F	% ≥ 1:61	99	100%	(96–100)	108	100%	(97–100)	94	100%	(96–100)
	OPA GMT	99	2309	(1679–2693)	108	3691	(3230–4217)	94	3128	(2604–3757)
9V	% ≥ 1:151	105	91%	(84–96)	109	95%	(90–98)	103	96%	(91–99)
	OPA GMT	105	981	(788–1220)	109	1386	(1109–1731)	103	1203	(966–1497)
14	% ≥ 1:62	107	100%	(97–100)	111	97%	(92–99)	105	99%	(95–100)
	OPA GMT	107	1248	(1039–1500)	111	1492	(1203–1850)	105	1160	(937–1437)
18C	% ≥ 1:115	108	99%	(95–100)	114	100%	(97–100)	106	98%	(94–100)
	OPA GMT	108	733	(617–872)	114	1091	(947–1257)	106	916	(763–1100)
19A	% ≥ 1:31	96	99%	(94–100)	102	100%	(96–100)	93	100%	(96–100)
	OPA GMT	96	936	(766–1144)	102	993	(832–1186)	93	1409	(1178–1686)
19F	% ≥ 1:113	106	97%	(92–99)	112	98%	(94–100)	105	98%	(93–100)
	OPA GMT	106	394	(780–1133)	112	1122	(949–1326)	105	917	(754–1115)
23F	% ≥ 1:55	100	100%	(96–100)	107	98%	(93–100)	86	100%	(96–100)
	OPA GMT	100	2089	(1775–2459)	107	2087	(1714–2541)	86	2414	(1981–2942)
Unique V114 serotypes										
22F	% ≥ 1:15	79	100%	(95–100)	84	100%	(96–100)	61	20%	(11–32)
	OPA GMT	79	1814	(1501–2192)	84	1817	(1549–2131)	61	12	(9–18)
33F	% ≥ 1:20	88	93%	(86–97)	86	95%	(89–99)	87	47%	(36–58)
	OPA GMT	88	3779	(2496–5722)	86	3677	(2512–5381)	87	61	(38–97)

however, the difference was more pronounced at the PD3 time point than at the PD4 time point. The observed difference in serotype-specific IgG GMCs may not be clinically relevant as >90% of subjects across the 3 vaccination groups have IgG GMCs >0.35 µg/mL, significantly higher than the estimated IgG threshold value needed for protection against IPD caused by serotype 6A of approximately 0.16 µg/mL. Serotype-specific variability was noted, and GMCs were lower for some serotypes in V114 compared with PCV13, similar to the variability observed when PCV13 was compared with PCV7.[42] Importantly, this study was not powered to assess the significance of the differences in GMCs. Additionally, the GMCs represent an average concentration and may be influenced by outliers in a clinical trial. For these reasons, reverse cumulative distribution curves are included to provide a more comprehensive representation of clinical vaccine performance for all serotypes in V114 and PCV13.[21]

It is important to note the high response rates and IgG GMCs for the 2 serotypes unique to V114 (22F and 33F), as these serotypes are responsible for an increased percentage of IPD cases in children and adults in countries where PCVs are included in the infant immunization program. Including these 2 additional serotypes 22F and 33F in a pneumococcal conjugate vaccine is a relevant approach to address the overall global burden of pneumococcal disease.

While there was a higher incidence of solicited injection-site pain observed with V114 PD1 and PD2, this finding was not observed at the other postdose time points. Rates of systemic AEs, elevated temperatures and SAEs were generally comparable across the 3 vaccination groups and of mild-to-moderate intensity, and the safety profile observed in this study was consistent with safety reported in previous V114 pediatric trials.[31,32] The majority of the reported injection-site and systemic AEs in all 3 vaccination groups were transient and mild-to-moderate intensity. Overall, vaccination with V114 was generally well tolerated, with a safety profile generally comparable to PCV13.

These study results showed reproducibility of immune response rates of the new V114 formulation demonstrated in an earlier study.[31,32] Where earlier studies investigated different formulations of polysaccharide and adjuvant concentrations, the results from this study give confidence to the current formulation and demonstrate manufacturing consistency. Additionally, the results were reproduced in a larger, geographically diverse patient population, thus increasing generalizability. Similarly, acceptable immune responses with this formulation have also been demonstrated in adult populations 50 years of age and older.[39,43]

The results of this study are limited to immunogenicity because noninferiority for the 13 serotypes shared by V114 and PCV13 was demonstrated based on the difference in response rates using the World Health Organization-accepted threshold value of 0.35 µg/mL, which does represent a correlate of efficacy against IPD for many serotypes included in PCV13. Additionally, while high response rates and GMCs were observed for serotypes 22F and 33F, there are no data on the antibody threshold needed to protect against IPD due to these serotypes.

In conjunction with comparable general tolerability and an acceptable safety profile, V114 demonstrated noninferior immune responses for all serotypes in common with PCV13 and higher immune responses for the 2 unique serotypes, thus supporting the continued evaluation of this more broadly based PCV in phase 3 development.

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