Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Healthy Infants in the United States

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BACKGROUND

- Pneumococcal disease is a major global health concern that can manifest as invasive (ie, bacteremia, meningitis, bacteremic pneumonia) and noninvasive (ie, otitis media, nonbacteremic pneumonia) disease.[1]
  - Children <5 years of age are at increased risk of disease and generally exhibit a more rapid progression.[2]
- The introduction and widespread use of the 7-valent pneumococcal conjugate vaccine (PCV7) followed by the 13-valent PCV (PCV13) have significantly reduced pneumococcal disease burden.[3-7]
  - However, a substantial burden of pneumococcal disease caused by non-PCV13 serotypes remains; expanded-valent PCVs have the potential to address this unmet need.[8,9]
- A 20-valent PCV (PCV20), which includes all components of PCV13 along with capsular polysaccharide conjugates for 7 additional serotypes, is currently in development.
  - These 7 additional serotypes were chosen based on their prevalence as a cause of invasive pneumococcal disease, wide geographic distribution, and other factors supporting inclusion (eg, antibiotic resistance, disease severity).[1,8-14]

OBJECTIVE

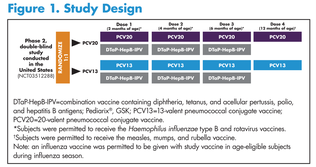
- To evaluate the safety and immunogenicity of PCV20 in healthy infants

METHODS

Study Design and Subjects

- In this phase 2, multicenter, randomized, active-controlled, double-blind study (NCT03512288), healthy infants were randomized 1:1 to receive either PCV20 or PCV13 at 2, 4, 6, and 12 months of age in combination with other routine infant vaccines (Doses 1, 2, 3, and 4, respectively; **Figure 1**).

Figure 1. Study Design



DTaP-HepB-IPV=combination vaccine containing diphtheria, tetanus, and acellular pertussis, polio, and hepatitis B antigens; Pediarix®, GSK; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
*Subjects were permitted to receive the *Haemophilus influenzae* type B and rotavirus vaccines.
†Subjects were permitted to receive the measles, mumps, and rubella vaccine.
Note: an influenza vaccine was permitted to be given with study vaccine in age-eligible subjects during influenza season.

Safety

- Local reactions and systemic events within 7 days of each dose were reported daily using an electronic diary filled out by each subject's parent/legal representative.
- Adverse events (AEs) were collected from Dose 1 to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4.
- Serious AEs (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) were collected from Dose 1 to 6 months after Dose 4.

Immunogenicity

- Immunogenicity was assessed by anticapsular immunoglobulin G (IgG) concentrations measured by the Pfizer Luminex assay and by opsonophagocytic activity (OPA) titers 1 month after Dose 3, before Dose 4, and 1 month after Dose 4.

METHODS (continued)

Statistical Analysis

- All analyses were descriptive, with no hypothesis tests or formal between-group comparisons for safety or immunogenicity results.
- Safety endpoints were summarized as percentages along with associated 2-sided 95% CIs calculated by the Clopper-Pearson method.
- The IgG geometric mean concentrations (GMCs) and OPA geometric mean titers (GMTs) with associated 2-sided 95% CIs based on the Student *t* distribution were calculated at each time point.
- The IgG geometric mean fold rises (GMFRs) from 1 month after Dose 3 to 1 month after Dose 4 along with the associated 2-sided 95% CIs based on Student *t* distribution were calculated.
- Percentages of participants achieving prespecified IgG concentrations (≥0.35 µg/mL or equivalent Luminex level[15,16]) and the Clopper-Pearson 2-sided 95% CIs at 1 month after Dose 3 were summarized.

RESULTS

Study Population

- 232 and 228 infants were randomized to the PCV20 and PCV13 groups, respectively.
  - 89.3% and 82.8% completed the 1-month visits after Doses 3 and 4, respectively.
- Demographic characteristics were similar between groups **(Table 1)**.

Table 1. Demographics

	PCV20 (n*=232)	PCV13 (n*=228)
	%	%
Male	51.7	49.6
Race†		
White	69.4	75
Black or African American	15.1	12.7
Asian	3.9	2.2
American Indian or Alaska Native	1.7	1.3
Native Hawaiian or other Pacific Islander	0.4	1.3
Multiracial	9.5	6.6
Not reported	0.0	0.9
Ethnicity		
Hispanic/Latino	17.7	17.5
Age at Dose 1, d‡		
Mean (SD)	64.5 (8.1)	64.5 (6.7)
Median	64	64
Min, max	44, 95	45, 89

PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
*=number of randomized subjects in the specified group.
†Subjects whose race is not in the listed categories are included in the "not reported" category.
‡For subjects randomized but not vaccinated, age is calculated using enrollment date instead of the date of first dose.

RESULTS (continued)

Safety

- Local reactions and systemic events are summarized in **Figure 2**.
- AEs, immediate AEs, SAEs, and NDCMCs are summarized in **Table 2**.

Immunogenicity

Immunoglobulin G

13 Matched Serotypes

- Robust immune responses were observed after PCV20, and IgG GMCs at 1 month after Dose 3 and before and 1 month after Dose 4 of either vaccine were similar **(Figure 3A and 3B)**.
  - IgG GMFRs from 1 month after Dose 3 to 1 month after Dose 4 demonstrate that both PCV20 and PCV13 show similar boosting **(Figure 3C)**.

7 Additional Serotypes

- IgG GMCs at 1 month after Doses 3 and 4 were increased in the PCV20 group and remained low in the PCV13 group **(Figure 4A and 4B)**.
  - IgG GMFRs from 1 month after dose 3 to 1 month after dose 4 are shown in **Figure 4C**.

Prespecified IgG Concentrations for the 13 Matched and 7 Additional Serotypes

- Percentages of subjects achieving prespecified IgG concentrations and associated 95% CIs at 1 month after Dose 3 are shown in **Figure 5**.

Distribution Curves of IgG Concentrations for the 13 Matched Serotypes

- The distributions of IgG concentrations 1 month after Dose 3 are presented in **Figure 6**.
- Overall, the IgG concentrations to the 13 matched serotypes were slightly lower in the PCV20 group; however, the decrement in concentrations was small and robust responses were induced to all 20 serotypes.

Opsonophagocytic Activity

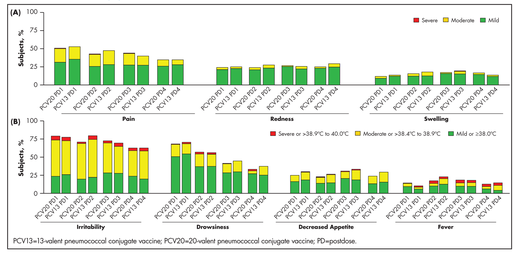
- OPA responses were observed for all 20 vaccine serotypes at 1 month after Dose 3 of PCV20 **(Figure 7)**.

Table 2. Summary of Adverse Events in the Safety Population

Type of AE Time Point Relationship	PCV20 n*	PCV20 %	PCV20 95% CI†	PCV13 n*	PCV13 %	PCV13 95% CI†
AE						
Dose 1 to 1 mo after Dose 3‡	141	61.0	54.4, 67.4	128	56.4	49.7, 62.9
Related§	5	2.2	0.7, 5.0	3	1.3	0.3, 3.8
Dose 4 to 1 mo after Dose 4‖	36	18.3	13.1, 24.4	49	25.3	19.3, 32.0
Related§	2	1.0	0.1, 3.6	3	1.5	0.3, 4.5
Immediate AE¶						
Dose 1‡	1	0.4	0.0, 2.4	0	0.0	0.0, 1.6
Dose 2#	1	0.5	0.0, 2.5	0	0.0	0.0, 1.7
Dose 3#	2	1.0	0.1, 3.4	0	0.0	0.0, 1.8
SAE						
Entire study**	12	5.2	2.7, 8.9	5	2.2	0.7, 5.1
Related§	0	0	0	0	0	0
NDCMC						
Entire study**	12	5.2	2.7, 8.9	8	3.5	1.5, 6.8
Deaths						
Entire study**	0	0	0	0	0	0

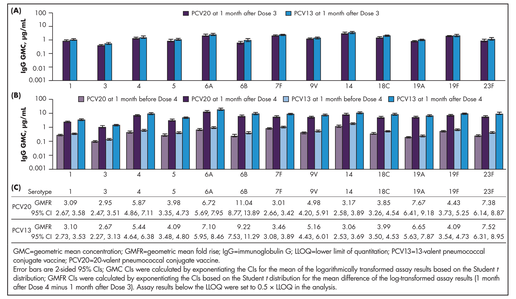
AE=adverse event; NDCMC=newly diagnosed chronic medical condition; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine; SAE=serious adverse event.
*=number of participants reporting ≥1 occurrence of the specified event.
†Exact 95% CIs were calculated using the Clopper and Pearson method.
‡Denominators used in the percentage calculations: PCV20, n=231; PCV13, n=227.
§Denominators used in the percentage calculations: PCV20, n=197; PCV13, n=194.
¶Occurring within 30 min of vaccination.
‖Denominators used in the percentage calculations: PCV20, n=221; PCV13, n=213.
#Denominators used in the percentage calculations: PCV20, n=210; PCV13, n=206.
**Denominators used in the percentage calculations: PCV20, n=232; PCV13, n=228.

Figure 2. Percentages of Subjects Experiencing Local Reactions (A) and Systemic Events (B) After Each Dose



PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine; PD=postdose.

Figure 3. IgG GMCs for the 13 Matched Serotypes (A) at 1 Month After Dose 3 and (B) 1 Month After Dose 4 and (C) GMFRs from 1 month after Dose 3 to 1 month after Dose 4

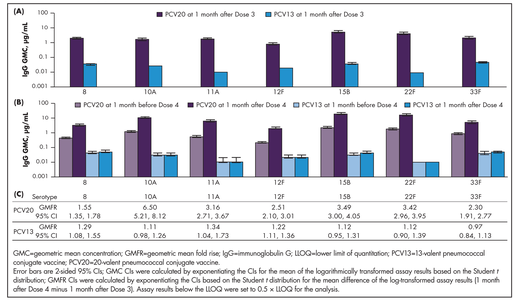


(C)

Serotype		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV20	GMFR	3.09	2.95	5.87	3.98	6.72	11.04	3.01	4.98	3.17	3.85	7.67	4.43	7.38
	95% CI	2.67, 3.58	2.47, 3.51	4.86, 7.11	3.35, 4.73	5.69, 7.95	8.77, 13.89	2.66, 3.42	4.20, 5.91	2.58, 3.89	3.26, 4.54	6.41, 9.18	3.73, 5.25	6.14, 8.87
PCV13	GMFR	3.10	2.67	5.44	4.09	7.10	9.22	3.46	5.16	3.06	3.99	6.65	4.09	7.52
	95% CI	2.73, 3.53	2.27, 3.13	4.64, 6.38	3.48, 4.80	5.95, 8.46	7.53, 11.29	3.08, 3.89	4.43, 6.01	2.53, 3.69	3.50, 4.53	5.63, 7.87	3.54, 4.73	6.31, 8.95

GMC=geometric mean concentration; GMFR=geometric mean fold rise; IgG=immunoglobulin G; LLOQ=lower limit of quantitation; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
Error bars are 2-sided 95% CIs; GMC CIs were calculated by exponentiating the CIs for the mean of the logarithmically transformed assay results based on the Student *t* distribution; GMFR CIs were calculated by exponentiating the CIs based on the Student *t* distribution for the mean difference of the log-transformed assay results (1 month after Dose 4 minus 1 month after Dose 3). Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

Figure 4. IgG GMCs for the 7 Additional Serotypes (A) at 1 Month After Dose 3 and (B) and 1 Month After Dose 4 and (C) GMFRs for the 7 Additional Serotypes from 1 Month after Dose 3 to 1 Month after Dose 4

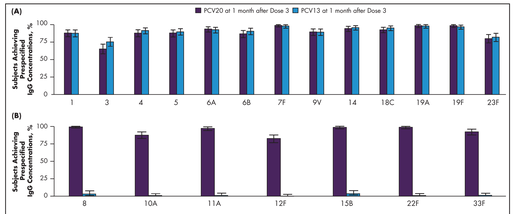


(C)

Serotype		8	10A	11A	12F	15B	22F	33F
PCV20	GMFR	1.55	6.50	3.16	2.51	3.49	3.42	2.30
	95% CI	1.35, 1.78	5.21, 8.12	2.71, 3.67	2.10, 3.01	3.00, 4.05	2.96, 3.95	1.91, 2.77
PCV13	GMFR	1.29	1.11	1.34	1.22	1.12	1.12	0.97
	95% CI	1.08, 1.55	0.98, 1.26	1.04, 1.73	1.11, 1.36	0.95, 1.31	0.90, 1.39	0.84, 1.13

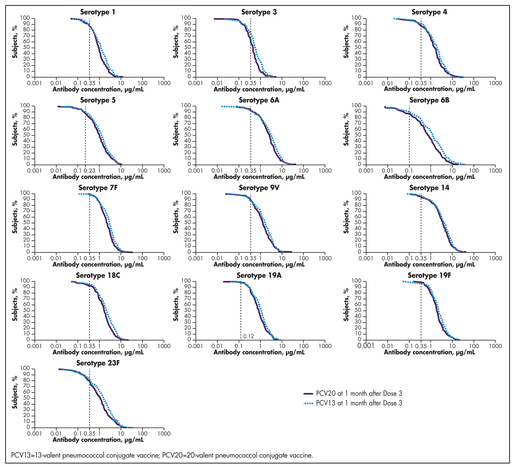
GMC=geometric mean concentration; GMFR=geometric mean fold rise; IgG=immunoglobulin G; LLOQ=lower limit of quantitation; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
Error bars are 2-sided 95% CIs; GMC CIs were calculated by exponentiating the CIs for the mean of the logarithmically transformed assay results based on the Student *t* distribution; GMFR CIs were calculated by exponentiating the CIs based on the Student *t* distribution for the mean difference of the log-transformed assay results (1 month after Dose 4 minus 1 month after Dose 3). Assay results below the LLOQ were set to 0.5 × LLOQ for the analysis.

Figure 5. Percentages of Subjects Achieving Prespecified IgG Concentrations for (A) the 13 Matched Serotypes and (B) 7 Additional Serotypes at 1 Month After Dose 3



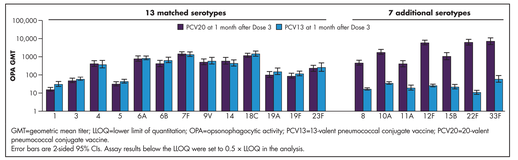
IgG=immunoglobulin G; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
Error bars are 2-sided 95% CIs.

Figure 6. Reverse Cumulative Distribution Curves for the 13 Matched Serotypes at 1 Month After Dose 3



PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.

Figure 7. OPA GMTs for the 13 Matched Serotypes and 7 Additional Serotypes at 1 Month After Dose 3



GMT=geometric mean titer; LLOQ=lower limit of quantitation; OPA=opsonophagocytic activity; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
Error bars are 2-sided 95% CIs. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

CONCLUSIONS

- **PCV20 was well tolerated, with a safety profile similar to PCV13.**
- **PCV20 induced robust immune responses to all 20 serotypes.**
  - IgG concentrations after PCV20 were similar to the licensed vaccine (PCV13) for the 13 matched serotypes.
  - Robust IgG responses to the 7 additional serotypes were observed.
  - Boosting of all 20 serotypes was observed after Dose 4, providing evidence that immune memory was elicited.
  - The immune responses were also associated with functional opsonic killing activity.
- **These findings supported US Food and Drug Administration breakthrough designation, which helps expedite vaccine development and review based on the vaccine's potential to be a substantial improvement over available therapy for prevention of serious disease, and also supported further development of PCV20 in the pediatric population.**

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