A Randomized Phase 1 Study of a Novel Pneumococcal Conjugate Vaccine in Healthy Japanese Adults in the United States

David Fitz-Patrick,[1] Mariano Young, Jr,[2] Daniel A. Scott,[2] Ingrid Scully,[3] Gary Baugher,[2] Yahong Peng,[2] Kathrin U. Jansen,[3] William C. Gruber,[3] Wendy Watson[2]

[1]East-West Medical Research Institute, Honolulu, HI, USA; [2]Pfizer Inc, Collegeville, PA, USA; [3]Pfizer Inc, Pearl River, NY, USA

For more information please contact: Mariano Young, Jr., MD, Vaccine Clinical Research and Development, Pfizer Inc, Email: Mariano.YoungJR@pfizer.com

BACKGROUND

- *Streptococcus pneumoniae* infection is a significant public health concern worldwide.[1]
- Two types of vaccines target pneumococcal disease:[2]
  - The 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax®, Merck and Co., Inc., Whitehouse Station, NJ), which contains unconjugated capsular polysaccharides, elicits a T-cell–independent response and therefore does not induce long-lasting immunity.[2,3]
    - Studies in older adults have been inconclusive or contradictory regarding protection of noninvasive disease, including nonbacteremic pneumococcal pneumonia.[4-6]
  - Pneumococcal conjugate vaccines (PCVs), including the 13-valent PCV (PCV13; Prevenar 13®, Pfizer Inc, New York, NY), contain capsular polysaccharides each covalently linked to an immunogenic protein, resulting in a robust T-cell–dependent response that induces immunologic memory.[3]
    - PCV13 has demonstrated efficacy and effectiveness against pneumococcal pneumonia (bacteremic and nonbacteremic) in older adults.[7,8]
- PPSV23 is routinely recommended for adults ≥65 years of age in Japan who are at increased risk of pneumococcal disease.[9]
  - Despite routine PPSV23 recommendations in adults, 66% of invasive pneumococcal disease cases among adults in Japan occurring between April 2013 and March 2015 were caused by PPSV23 serotypes.[10]
    - 22% of cases were attributed to serotypes contained in PPSV23 but not PCV13.[10]
- To expand serotype coverage with the immunologic advantages of a conjugate vaccine, a 20-valent PCV (PCV20) has been developed.
  - PCV20 contains all the components of PCV13 as well as polysaccharide conjugates for 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F).
  - PCV20 was well tolerated and immunogenic for all 20 vaccine serotypes in phase 1 and 2 studies in US adults.[11,12]
  - This phase 1b clinical study evaluated PCV20 in Japanese adults to support further global development.

OBJECTIVE

- To describe the safety profile of PCV20 in the study population
- To describe the immunogenicity of PCV20 in the study population

METHODS

Study Design and Subjects

- This phase 1b, randomized, controlled, double-blind study enrolled 18 to 49-year old healthy Japanese adults defined as Japanese born in Japan, with both parents and 4 grandparents who were born in Japan (family tree by history), and who have not lived outside of Japan for more than 5 years total (confirmed by passport or interview) residing in the United States (NCT03642847). Subjects with prior pneumococcal vaccination were excluded.
- Subjects were randomized 1:1:1 to receive a single dose of PCV20, a different investigational vaccine, or PCV13 (control) administered intramuscularly.
  - Only PCV20 and PCV13 data will be presented here.

Safety

- Local reactions, fever, and other systemic events, and the use of antipyretic/pain medication were recorded for 14 days after vaccination.
- Adverse events (AEs) were collected from the time of informed consent through 1 month after vaccination, and serious AEs (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) were collected from the time of informed consent through 6 months after vaccination.

Immunogenicity

- Blood samples were obtained prior to and 1 month after vaccination for measurement of opsonophagocytic activity (OPA) titers to the 20 vaccine serotypes.

Statistical Analyses

- The study population size was not based on any formal statistical hypothesis testing.
- OPA geometric mean titers (GMTs) and OPA geometric mean fold rises (GMFRs) and 95% CIs at each time point (OPA GMTs) and ratios from before to 1 month after vaccination (GMFRs) were obtained by calculating the means and CIs in natural log scale, then exponentiating the results; CIs were based on the Student *t* distribution.

RESULTS

Study Population

- 70 Japanese adults were included, with 35 subjects randomized to PCV20 and 35 to PCV13.
  - 1 subject in PCV13 did not meet eligibility criteria and was not vaccinated.
- Baseline characteristics were similar between vaccine groups **(Table 1)**.

Safety

- Local reactions and systemic events were generally mild or moderate in severity across all the vaccine groups **(Figure 1)**.
  - The most frequent local reaction was pain at the injection site (PCV20, 77.1%; PCV13, 79.4%).
  - The most frequent systemic event was muscle pain (PCV20, 57.1%; PCV13, 52.9%).
  - 1 subject experienced fever of 38.8°C of 1-day duration; no other fevers were reported.
- 2 subjects (5.7%) in the PCV20 group reported AEs; 1 AE was considered related to vaccine (injection site erythema and swelling; **Table 2**).
- No severe AEs, SAEs, safety-related withdrawals, NDCMCs, or deaths were reported **(Table 2)**.

Immunogenicity

- OPA responses were elicited to all 20 serotypes in the PCV20 group **(Figures 2 and 3)** and all 13 serotypes in the PCV13 group **(Figure 2)**.
- OPA GMFRs from before to 1 month after PCV20 ranged from 6.1-fold (serotypes 3, 11A) to 150.7-fold (serotype 8) for the 20 vaccine serotypes **(Figures 2 and 3)**.

Table 1. Demographics

Demographic	Vaccine Group: PCV20 (n=35)	Vaccine Group: PCV13 (n=34)
Men, n (%)	15 (42.9)	14 (41.2)
Japanese, n (%)	35 (100.0)	34 (100)
Age at vaccination, y		
Mean ± SD	29.9±10.29	31.4±9.99
Median (range)	28.0 (18–47)	30.5 (18–49)

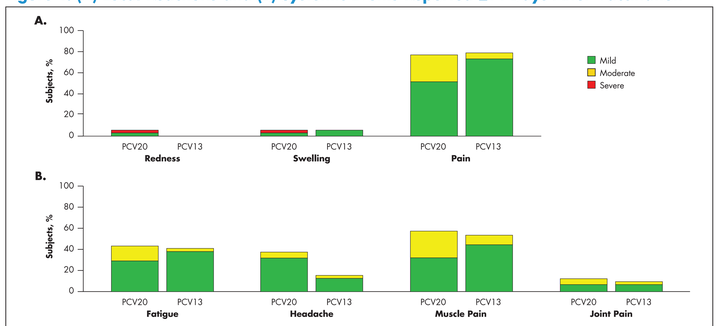
PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.

Table 2. Summary of Adverse Events Through 1 Month After Vaccination

AE type	Vaccine Group: PCV20 (N[a]=35) n[b] (%)	Vaccine Group: PCV13 (N[a]=34) n[b] (%)
Any AE	2 (5.7)	3 (8.8)
Related	1 (2.9)	0
Severe	0	0
SAE	0	0
NDCMC	0	0

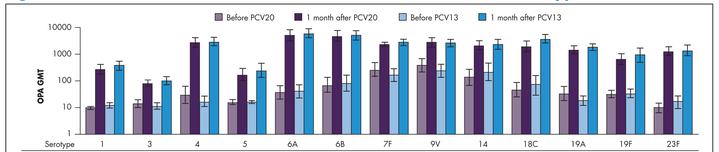
AE=adverse event; NDCMC=newly diagnosed chronic medical condition; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine; SAE=serious adverse event.
[a]N=number of subjects in the specified group.
[b]n=number of subjects reporting at least 1 occurrence of the specified event.

Figure 1. (A) Local Reactions and (B) Systemic Events Reported ≤14 Days After Vaccination



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

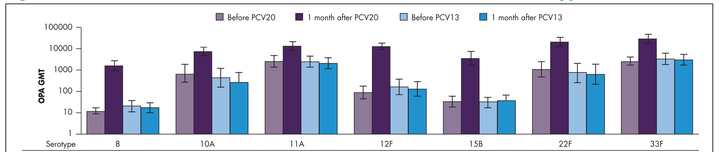
Figure 2. Pneumococcal OPA GMTs and GMFRs for the 13 Matched Serotypes



	Serotype	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV20	GMFR	29.1	6.1	96.3	11.0	144.7	65.0	8.4	7.5	11.9	38.8	46.3	20.3	136.9
	95% CI	18.9, 44.8	4.4, 8.5	40.5, 228.9	6.0, 20.0	70.7, 296.4	31.4, 134.2	4.4, 15.8	4.3, 13.1	5.8, 24.3	19.1, 78.8	24.3, 88.3	11.6, 35.7	79.2, 236.6
PCV13	GMFR	31.8	9.2	177.6	15.7	152.7	46.7	18.1	11.3	11.2	53.7	98.9	27.4	90.9
	95% CI	21.4, 47.2	6.4, 13.3	97.6, 323.3	8.5, 28.7	77.0, 302.6	22.2, 98.2	10.6, 30.8	6.8, 18.9	5.1, 24.5	24.0, 120.0	60.4, 162.1	14.5, 51.6	51.6, 160.1

GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantitation; OPA=opsonophagocytic activity; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
GMTs were calculated using all subjects with available data for the specified blood draw.
GMFRs were calculated using all subjects with available data from blood draws both before and after vaccination.

Figure 3. Pneumococcal OPA GMTs and GMFRs for the 7 Additional Serotypes



	Serotype	8	10A	11A	12F	15B	22F	33F
PCV20	GMFR	150.7	10.6	6.1	149.1	101.6	19.6	10.0
	95% CI	72.5, 313.3	4.5, 25.3	3.2, 11.6	68.0, 327.2	35.5, 291.0	8.4, 45.7	6.3, 15.6
PCV13	GMFR	0.9	0.7	0.7	1.0	1.3	1.3	0.9
	95% CI	0.6, 1.4	0.5, 1.1	0.6, 1.0	0.9, 1.0	0.9, 1.9	0.8, 2.1	0.7, 1.1

GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantitation; OPA=opsonophagocytic activity; PCV13=13-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine.
Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
GMTs were calculated using all subjects with available data for the specified blood draw.
GMFRs were calculated using all subjects with available data from blood draws both before and after vaccination.

CONCLUSIONS

- **A single dose of PCV20 was well tolerated and induced robust serotype-specific functional OPA immune responses in healthy Japanese adults 18–49 years of age consistent with that observed in prior studies.**
- **These results support continued clinical development of PCV20 in Japan and globally.**

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DISCLOSURES

DF received research funding from Pfizer Inc. MY, DAS, IS, GB, YP, KUJ, WCG, and WW are employees of Pfizer Inc and may hold stock and/or stock options.

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