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# Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 18–49 years of age, naive to 23-valent pneumococcal polysaccharide vaccine

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ABSTRACT

*Background:* Based on the success of vaccination with pneumococcal conjugate vaccines (PCVs) in children, recent studies have focused on PCVs in adults. Data from a randomized, double-blind study comparing the immunogenicity, tolerability, and safety of the 13-valent PCV (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in PPSV23-naive adults 60–64 years of age have been published. The same study also included a cohort of adults aged 18–49 years that received open-label PCV13. The purpose of this cohort was to examine the immunogenicity, safety, and tolerability of PCV13 in adult subjects 18–49 years of age compared with adults 60–64 years of age for whom PCV13 is approved.
*Methods:* Adults naive to PPSV23 were grouped by age into 2 cohorts: 18–49 years ($n$ = 899; further stratified by age into 3 subgroups 18–29, 30–39, and 40–49 years) and 60–64 years ($n$ = 417). All subjects received 1 dose of PCV13. In both age groups, immunogenicity was assessed by antipneumococcal opsonophagocytic activity (OPA) geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs) 1 month after vaccination. Safety and tolerability were evaluated.
*Results:* In adults aged 18–49 years, OPA GMTs and IgG GMCs were noninferior for all 13 serotypes and statistically significantly higher for all except 1 serotype (OPA GMT) and 5 serotypes (IgG GMCs) compared with adults 60–64 years. Immune responses were highest in the youngest age subgroup (18–29 years). Local reactions and systemic events were more common in adults 18–49 years compared with 60–64 years and were self-limited.
*Conclusion:* Immune responses to PCV13 are robust in adults ≥18 years of age, with highest responses observed in the youngest subgroup. Based on its safety and immunologic profile, PCV13 may serve an important therapeutic role in younger adults, particularly those with underlying medical conditions who have an increased risk of serious pneumococcal infections.



*Abbreviations:* AE, adverse event; CAP, community-acquired pneumonia; GMFR, geometric mean fold rise; GMT, geometric mean titer; IPD, invasive pneumococcal disease; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SAE, serious adverse event.

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## 1. Introduction

Invasive pneumococcal disease (IPD) remains a major cause of morbidity and mortality in adults ≥50 years of age [1]. Disease caused by *Streptococcus pneumoniae* most commonly manifests as bacteremic and nonbacteremic pneumonia, meningitis, and septicemia [1]. Although the incidence of IPD is generally greatest at the extreme ages of life, the incidence of pneumococcal disease and associated hospitalization and mortality rates in younger adults are substantial, especially among those with risk conditions including cardiovascular, pulmonary, and liver diseases, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, seizure or neuromuscular disorders, or diabetes mellitus [2–7]. Moreover, 2 or more risk conditions have been associated with substantial increases in the rates of pneumococcal pneumonia and IPD compared with healthy adults, with the rates of disease increasing across advancing age groups [4].

Vaccination of at-risk and high-risk young adults with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended in the United States and most European countries [8,9]. Although a number of randomized clinical trials and case-control studies have been published [10,11], the degree of protection afforded by PPSV23 remains unclear [12]. In the elderly population, PPSV23 offers some protection against IPD but has a moderate effect in the high-risk elderly and other high-risk adults; PPSV23 offers little or no protection against pneumonia [9,11,12]. In fact, some studies have demonstrated that PPSV23 administration is associated with reduced responses to subsequent administration of PPSV23 or pneumococcal conjugate vaccines (PCVs) [13–15].

In a recent study conducted in elderly adults, the 13-valent PCV (PCV13) was effective at reducing pneumococcal disease, particularly IPD, caused by serotypes contained in the vaccine; PCV13 also provides protection against pneumonia [16]. Immunocompetent older adults with chronic underlying diseases and healthy adults of the same age have been shown to mount a comparable immune response to PCV13 [17], suggesting that at-risk subjects may experience the same benefit from vaccination with PCV13 as healthy subjects [18]. Similar benefits of PCV13 are anticipated for younger adults 18 to 49 years of age.

Results from a randomized, double-blind study that compared the immunogenicity, tolerability, and safety of PCV13 and PPSV23 in PPSV23-naive adults 60–64 years of age have been published [17]. The study also included a cohort of adults aged 18–49 years that received open-label PCV13. The purpose of this cohort was to examine the immunogenicity, safety, and tolerability of PCV13 in adult subjects 18–49 years of age compared with adults 60–64 years of age for whom PCV13 is approved; the results of the comparison are presented here.

## 2. Methods

### 2.1. Study design

In this phase 3 study conducted at 25 centers, adults 18–64 years of age were stratified into 2 cohorts by age (18–49 and 60–64 years) and received a single administration of PCV13; the 18- to 49-year cohort was further stratified into 3 subgroups of subjects (18–29, 30–39, and 40–49 years of age). Serotype-specific immune responses in the 18- to 49-year cohort and each of the subgroups were compared with responses in the 60- to 64-year cohort 1 month and 1 year postvaccination. Safety and tolerability of PCV13 in the 18- to 49-year cohort was compared with the 60- to 64-year cohort. This study complied with the Declaration of Helsinki [19] and International Conference on Harmonisation Guidelines for Good Clinical Practice [20].

### 2.2. Study subjects

Subjects were generally healthy adults 18–64 years of age; subjects with stable, chronic, pre-existing medical conditions (e.g., cardiovascular, pulmonary, renal, or liver diseases including alcoholic liver disease and alcoholism, and diabetes mellitus) were eligible for the study. Women of childbearing potential could not be pregnant or breastfeeding and all subjects agreed to remain abstinent or use contraception. Subjects were excluded if they had serious chronic disorders; severe adverse reactions or hypersensitivity associated with a vaccine or vaccine component; receipt of blood or blood products 6 months before the study; immunization with diphtheria-containing vaccines within 6 months before administration of the study vaccination or anticipated vaccination before the study completion; or a previous vaccination with a pneumococcal vaccine at any time or any other vaccine (except influenza) ≤30 days before study vaccination. Influenza vaccine was permitted if administered ≥14 days before the study start.

### 2.3. Vaccine

PCV13 (Prevnar 13/Prevenar 13®, Wyeth Vaccines; Lot Numbers 7-5095-001A and 7-5095-005A) contains polysaccharide antigens corresponding to pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F. Individual polysaccharide antigens were conjugated to a nontoxic diphtheria toxin (cross-reactive material 197). Each single-dose syringe contained 0.5 mL with 2.2 μg of each pneumococcal serotype, except for 4.4 μg of serotype 6B. Each dose was formulated in 5.0 mM succinate and 0.85% sodium chloride at pH 5.8 with 0.125 mg aluminum as aluminum phosphate and 0.02% polysorbate 80. The vaccine was preservative-free and stored at 2–8 °C.

### 2.4. Study objectives

The primary immunogenicity objective of the study was to demonstrate that PCV13 immune responses 1 month after vaccination in subjects 18–49 years of age were noninferior to responses in subjects 60–64 years of age as measured by serotype-specific opsonophagocytic activity (OPA). Secondary immunogenicity objectives were to demonstrate that the immune responses to PCV13 serotypes in each of the age subgroups (18–29, 30–39, and 40–49 years) 1 month after PCV13 administration were noninferior to those in adults 60–64 years of age. Exploratory immunogenicity objectives included OPA and IgG persistence after 1 year in a subset of the 18- to 49-year age group and in subsets of each age subgroup, compared with a subset of adults 60–64 years of age, and IgG geometric mean concentrations (GMCs) after 1 month in a subset of adults 18–49 years of age and subsets of each age subgroup compared with a subset of adults 60–64 years of age. The safety objectives were to assess local and systemic events captured in an electronic diary, as well as adverse events (AEs) and serious AEs (SAEs) after vaccination.

### 2.5. Immunogenicity assessments

Blood samples for immunogenicity assessments were collected at enrollment and 1 month (29–43 days) and 1 year (351–379 days) after vaccination. OPA geometric mean titers (GMTs) to the 13 pneumococcal serotypes were quantified using serotype-specific OPA. Titers were defined as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of the assay bacteria, as previously described [17]. Titers below the lower limit of quantitation were set to a value of 1:4 [17]. Serum IgG concentrations to the 13 serotypes were determined by ELISA in