Vaccines and Related Biological Products Advisory Committee

November 16, 2011

FDA Briefing Document

Prevnar 13™ (PCV13):
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)
Applicant: Wyeth Pharmaceuticals Inc.

Tina Khoie, M.D., M.P.H.
Rosemary Tiernan, M.D., M.P.H
Nicolette deVore, Ph.D.

CBER/FDA

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1.0 General Information

Product name:

Proper name: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Trade name: Prevnar 13

Product composition: Each 0.5 mL dose contains:

- ~ 2.2 ug of each saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4 ug of serotype 6B individually conjugated to diphtheria cross-reacting material 197 (CRM_{197}) carrier protein. The total concentration of CRM_{197} is ~ 34 ug.
- 295 ug succinate buffer
- 125 ug aluminum as $AlPO_4$ adjuvant
- 100 ug polysorbate 80.

The vaccine contains no preservative.

Applicant: Wyeth Pharmaceuticals Inc.

Current Indications: Active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F and for the prevention of otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Prevnar 13 is approved for use in children 6 weeks through 5 years of age.

New Proposed Indication And Usage: Active immunization for the prevention of pneumococcal disease (including pneumonia and invasive disease) in adults 50 years of age and older caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

Dosage Form and Route of Administration: Suspension for intramuscular injection

2.0 Executive Summary

Wyeth Pharmaceuticals Inc. has submitted a Biologics License Application Supplement (BLS) to support the use of a single dose of Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein] (Prevnar 13) in adults aged 50 years and older. The proposed indication in this age group is the active immunization for the prevention of pneumococcal disease (including pneumonia and invasive disease) caused by *Streptococcus pneumoniae* serotypes contained in the vaccine. The approval of Prevnar 13 (PCV13) for use in adults would be based on an immunological surrogate endpoint through the Accelerated Approval Regulation [21 CFR 601.41]. This regulation applies to biologics intended to treat serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Pneumovax 23, which is the only pneumococcal vaccine licensed in the United States (U.S.) for use in adults, has not been demonstrated to be effective in the prevention of non-bacteremic pneumococcal pneumonia.[1,2] Non-bacteremic pneumococcal pneumonia continues to be a more common pneumococcal disease manifestation than invasive pneumococcal disease (IPD) in adults.[3,4] The Center for Biologics Evaluation and Research (CBER), therefore, considers protection of adults/elderly from non-bacteremic pneumococcal pneumonia or non-bacteremic pneumococcal pneumonia combined with protection from IPD to be a "meaningful therapeutic benefit over existing treatments."

Under the accelerated approval regulation, the Food and Drug Administration (FDA) has the authority to grant marketing approval based on adequate and well-controlled clinical trials establishing that a biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Opsonophagocytosis, mediated by antibodies and complement, is thought to be the main protective mechanism against pneumococcal disease *in vivo*. For pneumococcal conjugate vaccines, an evaluation of vaccine induced opsonophagocytic antibody titer (OPA activity) can serve as an outcome that is likely to predict clinical benefit, and as such, would meet the requirements of a surrogate for efficacy under the accelerated approval regulations (21 CFR 601.41).

The accelerated approval regulations require that the applicant study the biological product further to verify and describe its clinical benefit through adequate and well-controlled clinical trials. In order to demonstrate clinical benefit, the applicant is conducting a randomized (1:1), parallel-group, placebo-controlled clinical endpoint trial of Prevnar 13 in 85,000 community-dwelling adults aged 65 years and older in the Netherlands. The primary objective of the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA) is to establish the efficacy of PCV13 in the prevention of a first episode of vaccine-type pneumococcal pneumonia. Enrollment in this trial is complete, and results are expected to become available sometime in the next one to two years.

The clinical development program for Prevnar 13 in adults aged 50 years and older included two primary phase 3 immunogenicity trials (6115A1-004 and 6115A1-3005) for inferring effectiveness of a single dose of Prevnar 13 in adults 50 to 64 years of age and of a single dose in adults aged 70 years or older who previously received Pneumovax 23

at least 5 years prior. Pneumovax 23 (23vPS) was selected as an active-control because it is the only pneumococcal vaccine licensed for use in adults in the U.S., and it is the current standard of care in the target population. Effectiveness was inferred via measurement of functional antibodies to each of the thirteen serotypes contained in PCV13 by an OPA assay. In both pivotal studies, the primary endpoints were met and are summarized as follows: For the comparison of the OPA responses of PCV13 and 23vPS, the non-inferiority criterion required that the ratio of geometric mean titers (GMTs) (PCV13/23vPS) be greater than 0.5 for the 12 common serotypes (i.e., lower limit of the 2-sided 95% confidence interval (CI) for the GMT ratio (PCV13/23vPS) > 0.5). In study 004 in subjects 60 to 64 years of age, Prevnar 13 was shown to be non-inferior to Pneumovax 23 in inducing functional OPA against the 12 common serotypes (Table 3, page 23). Furthermore, for serotype 6A (which is unique to Prevnar 13), the success criterion for the comparison between PCV13 and 23vPS required that the difference in the proportion of subjects achieving at least a 4-fold increase in OPA titer be greater than 0 (i.e., lower limit of the 95% CI for the difference in the proportion of subjects achieving at least a 4-fold increase in OPA titer > 0). A statistically significantly greater proportion of Prevnar 13 recipients achieved functional anti-6A antibody responses compared to Pneumovax 23 recipients (Table 4, page 24). Together, PCV13 met all primary immunogenicity endpoints in study 004, evaluating subjects 60 to 64 years of age. In addition, for the 13 pneumococcal serotypes contained in PCV13, the criterion for demonstrating non-inferiority of a single dose of PCV13 in subjects 50-59 years of age compared to a single dose of PCV13 in subjects 60-64 years of age was also met (Table 5, page 25). Similarly, in study 3005, in subjects 70 years and older, the criterion for demonstrating non-inferiority of PCV13 compared to 23vPS was met for the 12 common serotypes (Table 17, page 41). In this study, for serotype 6A, the success criterion for the comparison between PCV13 and 23vPS was also met (Table 18, page 42).

Studies also evaluated, as exploratory analyses and/or secondary objectives, sequential administration of PCV13 and 23vPS using a 1 or 3.5 year interval and different age groups (60-64 year olds and > 70 year olds) in subjects with or without a prior immunization history with 23vPS as follows:

Study 6115A1-004 included exploratory analyses which evaluated sequential doses of PCV13 and 23vPS administered with a 3.5 year interval. Data summarizing the pneumococcal OPA GMTs in adults 50 to 64 years of age in study 004 can be found in Table 6 (page 27). The non-inferiority criterion for comparisons between groups given different regimens required that the ratio of the GMTs (group 1/group 2) be greater than 0.5 for the 12 common serotypes (i.e., lower limit of the 2-sided 95% CI for the GMT ratio (group 1/group 2) > 0.5). These data can be found in Tables 7 – 15 (pages 28 – 36) and are summarized below.

Group 1 regimen	Group 2 regimen	Table	Age	Results
PCV13/23vPS	23vPS	7	60-64	Non-inferiority observed for each of the 12 common serotypes
PCV13/23vPS	23vPS/23vPS	8	60-64	Non-inferiority observed for each of the 13 serotypes
PCV13/23vPS	PCV13	9	60-64	Non-inferiority observed for 10 of the 13 serotypes
23vPS/23vPS	23vPS	10	60-64	Non-inferiority observed for 7 of 13 serotypes
PCV13/PCV13	PCV13	11	60-64	Non-inferiority observed for 11 of the 13 serotypes
PCV13/PCV13	PCV13/23vPS	14	60-64	Non-inferiority observed for 7 of the 13 serotypes
PCV13/PCV13	23vPS/23vPS	15	60-64	Non-inferiority observed for each of the 13 serotypes
PCV13/PCV13	PCV13	12	50-59	Non-inferiority observed for 12 of 13 serotypes
60 to 64 yr olds given PCV13/PCV13	50 to 59 yr olds given PCV13/PCV13	13	50-59 and 60-64	Non-inferiority observed for 10 of the 13 serotypes

Sequential administration with a 1 year interval was also studied as a secondary objective in study 3005 in subjects aged ≥ 70 years who received 1 dose of 23vPS at least 5 years prior to enrollment. For the 12 common serotypes, the criterion for demonstrating non-inferiority of group 1 compared to group 2 was a lower limit of the 2-sided 95% CI for the GMT ratio (group 1/ group 2) exceeding 0.5. The success criterion for demonstrating statistically significantly greater OPA GMTs in group 1 compared to group 2 was a lower limit of the 95% CI for the OPA GMT ratio > 1.0. These comparisons are summarized below. For a summary of all data from this study, see Table 23 (Pages 47-48).

Group 1 regimen	Group 2 regimen	Table	Results
PCV13/PCV13	PCV13	19	Non-inferiority criterion was met for each of the 13 serotypes; statistically significantly greater responses achieved for 3 serotypes; statistically significantly lower responses achieved for 2 serotypes.
PCV13/PCV13	23vPS	20	Non-inferiority criterion was met for each of the 12 common serotypes; statistically significantly greater responses achieved for serotype 6A.
PCV13/PCV13	23vPS/PCV13	21	Statistically significantly greater responses observed for 11 of the 12 common serotypes.
23vPS/PCV13	PCV13	22	Statistically significantly lower responses were observed for each of the 13 serotypes.

Sequential administration of PCV13 and 23vPS, administered 1 year apart, was evaluated in 23vPS-naïve adults aged 60-64 years in study 6115A1-3010 using the same statistical criteria as above for non-inferiority and significantly greater GMTs. These comparisons are summarized below. For a summary of all OPA GMT data from this study, see Table 30 (pages 58-59).

Group 1 regimen	Group 2 regimen	Table	Results
PCV13/23vPS	23vPS	25	2-fold non-inferiority criterion was met for each of the 12 common serotypes; statistically significantly greater responses were achieved by 6 of the 12 common serotypes.
PCV13/23vPS	23vPS/PCV13	26	2-fold non-inferiority criterion was met for each of the 12 common serotypes; statistically significantly greater responses achieved by 11 of the 12 common serotypes.
PCV13	23vPS/PCV13	27	Statistically significantly greater criterion was met by each of the 12 common serotypes.
PCV13/PCV13	PCV13	28	Non-inferiority criterion was met by 9 of the 13 vaccine serotypes; statistically significantly greater responses achieved for 1 serotype; statistically significantly lower responses achieved for 7 of the 13 serotypes.
PCV13/23vPS	PCV13	29	Non-inferiority was met by 8 of the 12 common serotypes; statistically significantly greater responses achieved by 1 serotype; statistically significantly lower responses achieved by 8 of the 12 common serotypes.
23vPS/PCV13	23vPS	31	Non-inferiority observed for 10 of the 12 common serotypes; statistically significantly greater responses observed for 2 serotypes; statistically significantly lower responses observed for 10 of the 12 common serotypes.
PCV13/PCV13	PCV13/23vPS	32	Non-inferiority was observed for 8 of 12 common serotypes; statistically significantly lower responses observed by 5 of the 12 common serotypes; statistically significantly greater responses observed for 2 of the 12 common serotypes.

The results suggest that in the 23vPS-naïve 60 to 64 year age group, a 2 dose regimen consisting of an initial dose of PCV13 followed by 23vPS one year later elicits improved immune responses compared to an initial dose of 23vPS followed by PCV13. In addition, although the hyporesponsive phenomenon (i.e., an inability to mount an immune response following re-vaccination that is greater than or equal to the corresponding immune response induced after the primary vaccination) was observed following repeat administration of 23vPS and repeat administration of PCV13, the responses to a second dose of either pneumococcal vaccine resulted in a rise in functional antibody titer above the pre-dose 2 titers. Increasing the interval between repeat PCV13 vaccinations also seemed to improve the immune responses to the second dose among 60 to 64 year olds.

Additional supportive studies (6115A1-3001 and 6115A1-3008) evaluated co-administration of PCV13 with inactivated trivalent influenza vaccine (TIV) in subjects 50 to 59 and ≥ 65 years of age. Immune responses induced by each vaccine when administered concomitantly were compared to the corresponding immune responses induced by each vaccine when administered one month apart. The primary objectives compared immunoglobulin G (IgG) responses as determined in a standardized enzyme-linked immunosorbent assay (ELISA). While each of the TIV strains and pneumococcal serotypes in study 3001 (50 to 59 year olds) met non-inferiority criteria, the pneumococcal IgG geometric mean concentrations (GMCs) following co-administration with TIV were consistently lower than the values achieved when the two vaccines were administered 1 month apart (Table 35, page 65). In study 3008 (≥ 65 year olds), non-inferiority criteria were missed by a small margin for the A/H3N2 TIV strain and pneumococcal serotype 19F (Tables 40-41, pages 69-70). Because serotype-specific IgG may include a substantial component of non-functional antibodies, particularly in older adults, OPA is thought to be a more direct measure of protective response. Anti-pneumococcal OPA GMTs were compared in a subset of subjects in each study; non-inferiority was not observed by 3 to 5 pneumococcal serotypes (Tables 38 and 44, pages 67 and 72).

The Applicant evaluated the safety of PCV13 based on data from 6 adult studies in which a total of 5,667 subjects 50 to 93.5 years of age received at least one dose of PCV13. A total of 3,051 of the subjects were 65 years of age or older. Four of the six studies involved naïve subjects (subjects who had no prior receipt of Pneumovax23) and two studies involved adults who had previously received Pneumovax23.

Safety parameters evaluated in each study included unsolicited adverse events (AEs) and pre-specified, solicited adverse events (local reactions at the injection site and systemic events). Solicited local reactions included pain, redness, swelling, and limitation of arm movement. Solicited systemic events included fever, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain.

Overall, based on the results of the 6 clinical studies, the safety and reactogenicity profile of PCV13 has been shown to be acceptable in pneumococcal polysaccharide vaccine naïve and in pre-immunized adults. In the 6 clinical studies that were submitted to support the safety of the product, serious adverse events and deaths were observed at similar rates following immunization with PCV13 and Pneumovax 23 (pages 84-85). Limitations included the size of the safety database which allows detection of AEs occurring at a frequency no lower than 0.1%.

3.0 Introduction and Background

3.1 Epidemiology of Pneumococcal Infections in Adults

Streptococcus pneumoniae is a significant cause of morbidity and mortality among infants, young children, the elderly and persons who have certain underlying medical conditions. Pneumococcal disease can cause both invasive and non-invasive disease. IPD is defined by

isolation of *S. pneumoniae* from a normally sterile site (i.e. blood, cerebrospinal, pleural or peritoneal fluid). The most common IPD syndromes in adults aged 50 years and older include invasive (bacteremic) pneumonia, bacteremia without a focus, and meningitis. [6] Among all hospitalizations for community-acquired pneumonia (CAP), approximately 5 to 10% will have pneumococcal bacteremia.[7] Non-bacteremic pneumococcal pneumonia remains a more common disease manifestation, accounting for approximately 13-34% of pneumonia hospitalizations among adults.[3,4] *S. pneumoniae* is the leading cause of CAP across all severities in adults.[8]

Invasive Pneumococcal Disease Incidence Rates

Since the introduction of Prevnar (PCV7) in 2000, the rates of IPD caused by vaccine serotypes declined among U.S. children in the age group targeted by vaccination (direct effects) and among unimmunized older children and adults (indirect effect or herd immunity).[9] The impact of herd immunity following licensure of Prevnar is thought to have contributed to a reduction in the incidence of IPD among older adults.[9] Overall IPD rates due to all pneumococcal serotypes declined among adults ≥ 65 years of age from prior to 2000 through 2002 and leveled off from 2004 through 2007.[9] In this population, the incidence rate declined 37% from 60.1/100,000 in 1998-1999 to 37.9/100,000 in 2007.[9] The incidence of IPD among adults 50-64 years of age declined 18% from 24.0/100,000 in 1998-1999 to 19.8/100,000 in 2007.[9]

Despite these declines, pneumococcal infections remain an important cause of morbidity and mortality among older adults. Non-PCV7-type IPD incidence rates increased significantly between 2003 and 2007.[9] The incidence of IPD caused by the 16 serotypes included in 23vPS, but not in PCV7, increased by 28% (95% CI 12, 42) from 16.7 to 21.1 cases per 100,000 among adults 18 to 64 years of age.[9] Rates of IPD among adults ≥ 65 years of age caused by non-PCV7 types increased from 18.3/100,000 in 1998-1999 to 22.5/100,000 in 2007. Thus, in 2006-2007, about 15% of IPD cases among adults aged ≥ 65 years were due to the 11 pneumococcal strains included in 23vPS, which are not components of PCV13.[9,10]

Pneumococcal Pneumonia Incidence Rates

In contrast to the reduction in rates of IPD from indirect effects following the introduction of Prevnar, it is unclear whether a similar reduction in the rates of community acquired pneumonia from indirect effects (including pneumococcal CAP or all-cause CAP) has occurred, particularly among older adults.[11, 12]

Precise estimates on the rates of pneumococcal pneumonia and serotype-specific etiology have been challenging to measure, because available diagnostic tests are limited in their sensitivity or specificity.[13] Although a *S. pneumoniae* urine antigen detection assay based on the group carbohydrate antigen is available and serotype-specific urine and blood nucleic acid detection tests are in development, these have not gained widespread use. Without a positive culture from a sterile site, pneumonia is typically characterized as non-bacteremic; and given the generally infrequent use of tests to diagnose non-bacteremic pneumococcal pneumonia, most literature descriptions of CAP etiology are based on bacteremic pneumonia.

According to one publication which evaluated hospital discharge data from the Nationwide Inpatient Sample[4], the estimated rates of pneumococcal pneumonia (including bacteremic pneumonia) per 100,000 persons during the years 2001-2004 were as follows:

- ≤ 2 Years: 9.2
- 2-4 Years: 7.3
- 5-17 Years: 1.9
- 18-39 Years: 2.9
- 40-64 Years: 14.8
- ≥ 65 Years: 59.3

Risk Factors

In the U.S., individuals who are black or who are smokers are at higher risk of developing IPD compared to whites and non-smokers, respectively. Other risk factors recognized by the U.S. Advisory Committee on Immunization Practices (ACIP) include certain underlying medical conditions. The risk for IPD is greatest among persons who have congenital or acquired immunodeficiency, abnormal immune response, HIV infection, or functional or anatomic asplenia (i.e. sickle cell disease or congenital or surgical asplenia). Other underlying medical conditions associated with a higher risk of IPD include asthma, chronic cardiovascular (excluding hypertension), pulmonary, liver or renal disease, diabetes mellitus, nephritic syndrome, leukemias, lymphomas, Hodgkin disease, generalized malignancy, immunosuppressive drug use (including long-term systemic corticosteroids or radiation therapy), solid organ transplantation, multiple myeloma, alcoholism, and cerebrospinal fluid leaks. Alaska Native children and children among certain American Indian populations also have higher rates of IPD. Other risk factors or indications for pneumococcal vaccination include cigarette smoking, history of a cochlear implant, and certain living circumstances (such as residence in a nursing home).[14]

3.2 Currently Available Interventions

Two vaccines are currently available in the US to protect against pneumococcal disease. Pneumovax 23, the 23-valent pneumococcal polysaccharide vaccine (23vPS), was licensed in the U.S. in 1983, and it replaced a 14-valent formulation licensed in 1977. Pneumovax 23 is currently approved for routine use in persons ≥ 50 years of age and persons ≥ 2 years of age who are at increased risk of pneumococcal disease.[14] Each 0.5mL dose contains 25 μg of purified capsular polysaccharide from each of 23 pneumococcal serotypes. These polysaccharide antigens are thought to be T-independent antigens that stimulate mature B-lymphocytes, but not T-lymphocytes, and induce an immune response that is neither long-lasting nor anamnestic upon subsequent challenge. Pneumovax 23 is not approved for use in children < 2 years of age, because children in this age group generally have poor antibody responses to the vaccine. Data suggest that the 23vPS vaccine protects adults and the elderly against IPD, however no consistent vaccine effect has been observed for prevention of pneumonia.[1,2,14]

Routine re-vaccination with Pneumovax 23 is not currently included in the package insert as an approved use of the vaccine. The ACIP, which deliberates outside of the FDA

regulatory review process, provides recommendations regarding re-vaccination with 23vPS. Revaccination of immunocompetent persons previously vaccinated with 23vPS is not routinely recommended by ACIP; however, revaccination once, at least 5 years after receipt of the first dose, is recommended for persons ≥ 2 years of age who are at highest risk of serious pneumococcal infection.[14] According to ACIP, if prior vaccination status is unknown for high risk patients, then vaccination is indicated; in addition, all persons ≥ 65 years of age who have not received 23vPS within 5 years (and were < 65 at the time of vaccination), should receive another dose. Because data are not sufficient concerning the safety of 23vPS when administered ≥ 3 times, revaccination after a 2nd dose is not routinely recommended.[14]

Prevnar was the first pneumococcal conjugate vaccine licensed in the United States. Prevnar 13 was approved in the U.S. on February 24, 2010. Conjugation of pneumococcal saccharides to the CRM_{197} protein creates saccharide-protein complexes which are thought to be capable of inducing a T-dependent immune response; thus T-helper cells are stimulated leading to a booster response at re-exposure.

3.3 Immune Response Considerations

Hyporesponsiveness

Studies have suggested that a state of immune tolerance, or hyporesponsiveness, may develop following repeated administration of a bacterial polysaccharide in children and adults.[15-17] Hyporesponsiveness refers to an inability of an individual to mount an immune response following re-vaccination that is greater than or equal to the corresponding immune response induced after the primary vaccination. The underlying immune mechanism and clinical significance are not clearly understood. Immune responses following repeat doses of pneumococcal conjugate and pneumococcal polysaccharide vaccines in adults were evaluated in the immunogenicity studies submitted to this BLS.

Immune Response to Vaccines in Older Adults

The immune system undergoes characteristic changes with increasing age known as immunosenescence. This results in declining immune function, affecting cell types of both the innate and adaptive immune system and their interactions with each other.[4] With regards to inactivated vaccines, antibody titers appear to decline faster in elderly adults, and some studies suggest that the response to booster vaccination may depend on pre-booster antibody titers.[4, 18] Data also support the importance of early primary immunization to improve immunologic memory in old age.[4] Data from this BLS suggest the optimal vaccination schedule using both PCV13 and 23vPS will require considerations of age at first vaccination, the order in which the vaccines should be used, the interval between vaccinations, and the need for revaccination and other factors.[5]

3.4 Pneumococcal Conjugate Vaccine Regulatory Background

3.4.1 Licensure of PCV7

Prevnar, the first pneumococcal conjugate vaccine licensed in the U.S. on February 17, 2000, was approved by the FDA as a four dose series (2, 4, 6, and 12-15 months) for

active immunization to prevent invasive pneumococcal disease (IPD). The serotypes in the vaccine were originally selected because, at that time, they accounted for approximately 80% of IPD in young children in North America. A high level of efficacy (aggregated for the 7 serotypes) in preventing vaccine serotype IPD was demonstrated in a clinical endpoint vaccine efficacy trial in infants. On October 1, 2002, an additional Prevnar indication was approved for active immunization of infants and toddlers against otitis media caused by vaccine serotypes. Efficacy against otitis media was supported by data from an acute otitis media efficacy trial conducted in Finland, which involved tympanocentesis and bacterial cultures of middle ear fluid, as well as information on health care utilization for otitis media within a large Health Maintenance Organization (Northern California Kaiser Permanente). Safety outcomes were also evaluated in an observational post-marketing study that included 65,927 infants.

3.4.2 Licensure of PCV13 in Infants and Young Children

Given the wide use of Prevnar in the US, Europe and other parts of the world, it was considered impracticable to perform placebo-controlled studies for infants and toddlers. Therefore, the clinical development of Prevnar 13 involved an approach in which vaccine effectiveness against IPD was to be inferred from immunologic parameters. On March 8, 2001, the Vaccine and Related Biological Products Advisory Committee (VRBPAC) recommended that non-inferiority immunogenicity studies conducted in the U.S. comparing a pneumococcal conjugate candidate vaccine to Prevnar based on an antibody response quantified by ELISA would be an acceptable approach for inferring effectiveness against IPD for PCV13.

A series of expert consultations (including members of the FDA) convened by the WHO established a pneumococcal IgG antibody reference value of 0.35 µg/mL (by ELISA) for immunogenicity comparisons for all vaccine serotypes 1 month after three doses in infants. Limitations of the statistical modeling used to determine a single 0.35 µg/mL IgG antibody reference value include uncertain applicability across all serotypes, across different geographic regions, and among higher risk groups.[19] In addition, the 0.35 µg/mL IgG antibody reference value applies only to: (1) comparisons among infants after receipt of three doses of a pneumococcal conjugate vaccine, (2) the prevention of IPD, and (3) the population level rather than to an individual level.[19]

No consensus has emerged regarding the serologic criteria for assessing the effectiveness of pneumococcal conjugate vaccines in persons beyond 12-15 months of age. However, because the 0.35µg/mL reference value was intended primarily for the evaluation of immune responses in infants aged 6 months, evaluation of GMCs was viewed as more meaningful than seroresponse rates ≥ 0.35µg/mL in children beyond 7 months of age. In addition, functional OPA data were viewed as important supportive data for children in this age group and for adults.

Evaluation of functional antibodies, as measured in an OPA assay may be considered a preferable outcome measure, because opsonophagocytosis is thought to be the main protective mechanism *in vivo*. However, the OPA assay was more variable than the ELISA assay, and standardized OPA assay protocols were not yet available.

Nevertheless, a functional antibody assessment was recognized as important, and was thus included as an exploratory objective.

3.4.3 Licensure of Prevnar 13 in Adults

The approach to licensure of a pneumococcal conjugate vaccine for use in adults was discussed at a November 2005 VRBPAC meeting. Because of the low sensitivity and specificity of diagnostic tests for pneumococcal pneumonia at the time and the low incidence of IPD among older adults in the U.S., a very large sample size would have been needed to support an efficacy trial for the prevention of pneumonia and IPD. The applicant proposed that licensure be based solely on demonstration of non-inferiority of PCV13 compared to 23vPS based on functional (opsonophagocytic) antibody responses to the 12 commons serotypes contained in both vaccines. While the Committee agreed that an alternative vaccine to the 23-valent polysaccharide vaccine was desirable, the majority of Committee members favored a clinical endpoint efficacy study.

In December 2005, CBER determined that the initial approval of PCV13 for use in adults could be based on an immunological surrogate endpoint through the Accelerated Approval Regulation [21 CFR 601.41]. However, a condition of an accelerated approval is a requirement that the applicant study the biological product further to verify and describe its clinical benefit. Wyeth concurred with this proposal in March 2006, as the prospect of more sensitive and specific diagnostic tests for pneumococcal pneumonia made a clinical endpoint study more feasible.

The accelerated approval regulation gives FDA the authority to grant marketing approval based on adequate and well-controlled clinical trials establishing that a biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. This regulation applies to biologics intended to treat serious or life-threatening illnesses and that provide "meaningful therapeutic benefit to patients over existing treatments." Currently, the only pneumococcal vaccine licensed for use in adults is Pneumovax 23. However, its efficacy in the prevention of non-bacteremic pneumococcal pneumonia caused by vaccine serotypes has not been demonstrated.[1,2,14] Therefore, in this setting, CBER considers protection of adults/elderly from non-bacteremic pneumococcal pneumonia or non-bacteremic pneumococcal pneumonia combined with protection from invasive pneumococcal disease (IPD) to be a meaningful therapeutic benefit over existing treatments.

The clinical development plan for Prevnar 13 included two primary phase 3 trials designed to demonstrate non-inferiority of PCV13 compared to 23vPS based on anti-pneumococcal functional opsonophagocytic antibodies (OPA) to each of the thirteen serotypes contained in PCV13 (the designated surrogate for vaccine efficacy). Vaccine-naïve adults and adults who previously received 23vPS at least 5 years prior to study enrollment were evaluated separately in these two trials. Pneumovax 23 was selected as an active-control because it is the only pneumococcal vaccine licensed for use in adults and it is the current standard of care in the target population. Additional supportive studies evaluated sequential administration of PCV13 and 23vPS and co-administration of PCV13 with trivalent influenza vaccine.

In order to demonstrate clinical benefit, the applicant is currently conducting a randomized (1:1), parallel-group, placebo-controlled clinical endpoint trial of PCV13 in 85,000 community-dwelling adults aged 65 years and older in the Netherlands. Designing a placebo-controlled clinical endpoint study was considered feasible in the Netherlands because of the projected pneumococcal disease rates and the lack of a recommendation to use Pneumovax 23 in healthy adults in this country. Administration of Prevnar 13 in this study has been linked to the administration of routine annual influenza vaccination. The primary objective of this study, the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA), is to establish the efficacy of PCV13 in the prevention of a first episode of vaccine-type pneumococcal CAP. The study's secondary objectives include demonstrating efficacy of PCV13 in the prevention of a first episode of a first episode of vaccine-type IPD and the first episode of non-bacteremic vaccine-type pneumococcal CAP. This trial is ongoing, although enrollment is complete. The results of this study are anticipated to become available sometime in the next one to two years.

The indication that is being sought by the applicant is based on the current indication for 23vPS, which is the active immunization for the prevention of pneumococcal disease (including invasive disease and pneumonia).

Opsonophagocytic Antibody (OPA) and the Microcolony Opsonophagocytic Antibody Assay (mcOPA)

As indicated above, the efficacy of PCV13 in children was inferred from comparisons to Prevnar using IgG as measured by ELISA. It has been shown that pneumococcal glycoconjugate vaccines result in the production of functional antibody that correlates well with total IgG in infants.[19] However, the same has not been shown for older children and adults.[20] Therefore, vaccine serotype-specific IgG by ELISA was not considered to be an appropriate endpoint in adults.

Opsonophagocytic antibody, measured via an OPA assay, was selected as the surrogate immune marker for demonstrating the effectiveness of Prevnar 13 in adults.
Although there is no established correlate of protection against pneumococcal disease, OPA titers are associated with protection against invasive pneumococcal disease, and it is reasonably likely that OPA titers may be associated with protection against pneumonia.

The OPA assay is designed to assess the ability of functional antibody (from heat-inactivated human serum) to bind to pneumococcal bacteria in the presence of a functional complement source (baby rabbit serum) thereby facilitating bacterial engulfment and death by phagocytic human cell line (differentiated HL-60 cells).

OPA assays were used to measure functional antibody activity as an exploratory endpoint in the PCV13 infant program. The OPA assay used in the infant program, called dOPA, used the method of manually dribbling the final assay samples onto growth medium for bacterial colony formation and manual enumeration. This method was labor-intensive.

In order to support the high-throughput testing required with the use of OPA as a primary endpoint in the adult clinical development plan, the applicant simplified some of the

assay steps and introduced automation. This new assay, termed microcolony OPA (mcOPA), uses bacterial microcolonies for the enumeration of viable bacterial cells. Both assay methods use the same definition of an OPA titer – that is, the reciprocal of the lowest serum dilution that results in complement-dependent killing of 50% of the bacteria *in vitro* using a phagocytic cell line.

The changes introduced in the mcOPA assay required re-validation of the assay. As part of the assessment of the mcOPA assay, samples from the infant phase 3 study in Germany (6096A1-006) were tested using the assay. A statistical assessment of mcOPA and dOPA assay results found significant concordance between the findings of both assays. In contrast to the dOPA, which used the limit of the assay (1:8) as the LLOQ for all serotypes, a different LLOQ for each serotype was derived for the mcOPA assay based on validation data. As of yet, neither the dOPA nor the mcOPA assays are controlled by an external reference standard against which OPA results can be normalized. Thus, comparisons can not be made of serotype-specific OPA GMTs across different serotypes. Comparisons of serotype-specific OPA GMTs between Prevnar 13 and Pneumovax 23 recipients were viewed as more meaningful expression of the ability of Prevnar 13 to elicit opsonic activity.

Prevnar 13 Formulation for Adults

The Prevnar 13 formulation selected for use in adults is identical to the pediatric formulation approved in the original Prevnar 13 Biologics License Application (BLA). The dosage of each pneumococcal serotype within the vaccine is based on a trial (Wyeth study 92-5 conducted from 1992-1993, not included in this application but submitted to the original Prevnar BLA) that evaluated the immune response in 2-month old infants elicited by an experimental 5-valent vaccine that contained CRM_{197} conjugated to capsular pneumococcal serotypes 6B, 14, 18C, 19F, and 23F. The results from this trial demonstrated that a dosage of 2.0 µg per polysaccharide resulted in higher immune response to all 5 serotypes compared to a dosage of 0.5 µg per polysaccharide. In addition, the majority of the serotypes did not elicit an enhanced immune response with an increased dosage of 5.0 µg per polysaccharide. Thus, a dosage of 2.2 µg per polysaccharide, with the exception of serotype 6B (dosage 4.4 µg) was selected for Prevnar. The same dosage was maintained for the seven Prevnar serotypes in PCV13 and the 2.2 µg per polysaccharide dosage was selected for the additional 6 serotypes that were added to the PCV13 formulation.

The applicant noted that selection of the PCV13 formulation for adults, which contains aluminum and polysorbate 80, was based on results from study 6097A1-508 and the observation that inclusion of aluminum and polysorbate 80 resulted in protection of the product from protein aggregation and loss of antigenicity. Study 508 was a phase 1 study conducted in Germany with approximately 426 adults aged 70 years or older who had not previously been immunized with a pneumococcal vaccine. The standard pediatric dose and higher doses (2x and 4x the standard dose) were investigated in this study. The standard dose was selected by the applicant for trials in the adult PCV13 program based on immunogenicity and safety results.

Immunogenicity Endpoints

The primary endpoint in the Prevnar 13 adult clinical program included OPA titers one month post-vaccination; primary comparisons included an OPA geometric mean ratio (GMT) and the proportion achieving at least a 4-fold increase in OPA titer. Secondary endpoints included OPA titers or GMTs; secondary comparisons of interest included the proportion achieving an OPA titer of at least the serotype-specific LLOQ of the assay, OPA GMT ratio, and OPA geometric mean fold rise (GMFR). Exploratory endpoints included IgG GMCs 1 month post-vaccination and OPA titers 1 year post-vaccination.

Although serotype-specific polysaccharide IgG binding antibodies were measured for each of the 13 pneumococcal serotypes contained in PCV13 in the older adult development program (using the same standardized and validated ELISA method as for the infant BLA), the primary basis for approval in adults focuses on the results from OPA assays. Measurement of antibody response by an OPA assay is preferable over the ELISA assay, because non-functional antibodies are generated with increasing frequency as one ages. In addition, the ELISA assay results could be inaccurate regarding an effective immune response, since it measures both functional and non-functional antibodies.

In the studies evaluating sequential administration of 2 doses of pneumococcal vaccination, comparisons of post-dose 2 to post-dose 1 responses were viewed as clinically important information. This includes the evaluation of post-dose 1 and post-dose 2 responses among subjects within a single vaccine group as secondary and exploratory objectives. In these situations, GMFRs were used for the comparative analyses. GMFRs, which represent the fold rise in geometric mean titer or concentration from pre-vaccination levels, are not considered by CBER to be a sufficiently robust immunogenicity endpoint, because it has been suggested that GMFRs may not be able to fully control the pre-vaccination titer. However, these data are presented in the context of the GMTs. It is noted that the evaluation of GMFRs requires cautious interpretation, as a large GMFR does not necessarily indicate a superior immune response.[21]

4.0 Overview of Clinical Studies

The clinical section of the application contains study reports for 9 clinical studies.

Table 1. Clinical Studies to Support the Safety and Effectiveness of Prevnar 13 in Adults Aged ≥ 50 Years

Study No. / Country	Study Description and Primary Objective(s)	Age group (years)	Vaccination Group or Schedule	Number Vaccinated (as randomized)
Primary Non-inferiority Adult Studies				
6115A1-004[a] (USA)	P3 safety and immunogencity study in 23vPS naïve subjects[b] - Cohort 1: NI of PCV13 vs 23vPS - Cohort 2: NI of Cohort 2 vs Cohort 1	Cohort 1: 60-64 Cohort 2: 50-59	Year 0 schedule: Cohort 1: Single dose of PCV13 or 23vPS. Cohort 2: Single dose of PCV13. Yr 0 / Yr 3.5: Cohort 1: PCV13 / PCV13; or PCV13 / 23vPS; or 23vPS/ 23vPS Cohort 2: PCV13/PCV13	Yr 0: cohort 1/ cohort 2 PCV13: 417 / 404 23vPS: 414 / - Yr 0 / Yr 3.5: Cohort 1: 108; or 108; or 189 Cohort 2: 214
6115A1-3005 (USA, Sweden)	P3 safety and immunogenicity study in subjects with 1 prior dose of 23vPS ≥ 5 years prior to enrollment - NI of PCV13 vs 23vPS at year 0	≥ 70	Schedule: Yr 0 / Yr 1 Grp 1: PCV13/PCV13 Grp 2: 23vPS/PCV13	463 / 391 473 / 404
Final Formulation				
6115A1-500[c] (South Africa)	P2 study in 23vPS naïve subjects: - NI of PCV13-$AlPO_4$ vs PCV13+$AlPO_4$ - NI of PCV13 vs 23vPS, as a single dose	≥ 65	Schedule: Yr 0 / Yr 1 Grp 1: PCV13+$AlPO_4$ / 23vPS or PCV13+$AlPO_4$ Grp 2: PCV13-$AlPO_4$ / 23vPS Grp 3: 23vPS / None	309/ 131 or 136 304 / 273 301 / -
Supporting Studies				
6115A1-3000 (USA, Sweden, and Germany)	P3, non-controlled safety study in subjects pre-immunized with 1 or more doses of 23vPS ≥ 3 years prior to enrollment	≥ 68	PCV13	1049
6115A1-3010 (USA)	P3 safety and sequential use trial in 23vPS naïve: - NI of 23vPS given 1 year after PCV13 vs initial dose of 23vPS. - NI of 23vPS given 1 year after PCV13 vs PCV13 given 1 year after 23vPS	60-64	Schedule: Yr 0 / Yr 1 Grp 1.1: PCV13 / PCV13 Grp 1.2: PCV13 / 23vPS Grp 2.0: 23vPS / PCV13	161 266 223
6115A1-3001[d] (USA)	P3 safety and concomitant antigen study in 23vPS naïve subjects: - NI of TIV + PCV13 vs TIV alone - NI of TIV+PCV13 vs PCV13 alone (i.e. PCV13 one month after TIV)	50-59	Schedule: Day 1 / Day 29-43 Grp 1: PCV13+TIV / Placebo Grp 2: Placebo+TIV / PCV13	538 543

Study No. / Country	Study Description and Primary Objective(s)	Age group (years)	Vaccination Group or Schedule	Number Vaccinated (as randomized)
6115A1-3008 (Germany, the Netherlands, Belgium, and Hungary)	P3 safety[f] and concomitant antigen study in 23vPS naïve subjects: - NI of TIV + PCV13 vs TIV alone - NI of PCV13 + TIV vs PCV13 alone (1 month after TIV)	≥ 65	Schedule: Day 0 / Month 1 Grp 1: PCV13+TIV / Placebo Grp 2: Placebo+TIV / PCV13	577 575
Supporting Studies continued				
6115A1-3009 (South Africa)	P2, non-controlled study to evaluate PCV13 given 1 year after the sequence of PCV13+$AlPO_4$ /23vPS (Yr 0 / Yr 1) in study 6115A1-500 compared to the initial dose of PCV13 given in study 6115A1-500	≥ 65	Yr 0 / Yr 1 / Yr 2 PCV13 / 23vPS / PCV13	105
6097A1-508 (Germany)	P1 study to evaluate and select dose of a PCV for further investigation in the adult vaccine development program: - Safety of single injection of 1 of 3 doses of PCV vs 23vPS in ambulatory 23vPS naive elderly - Immunogenicity of 2nd dose of PCV or 23vPS 12 months after 1st injection - Immunogenicity of CRM197 pre-dose 1 and post-dose 2	≥ 70	Schedule: Yr 1 / Yr 2 Grp 1a: PCV7[e] / 23vPS Grp 1b: PCV7 / PCV7 Grp 2a: PCV7+PCV9(2x)[e] / 23vPS Grp 2b: PCV7+PCV9 / PCV7+PCV9 Grp 3a: 2xPCV7+2xPCV9 (4x) / 23vPS Grp 3b: 2xPCV7+2xPCV9 / 2xPCV7+2xPCV9 Grp 4: 23vPS/PCV7	Yr 1: PCV7: 105 2x: 110 4x: 108 23vPS: 103 Total: 426 Yr 2: PCV7/23vPS: 36 PCV7/PCV7: 43 2x/23vPS: 38 2x/2x: 38 4x/23vPS: 35 4x/4x : 40 23PS/PCV7 : 78 Total : 314

NI: non-inferiority
[a] Evaluation of cohort 3 (18 – 49 year old subjects) is ongoing.
[b] Cohort 2 was open-label. Cohort 1 involved a parallel-group and an active control, randomization (1:1) and modified double-blinding.
[c] The PCV13 formulation used in this study did not include polysorbate 80. PCV13 + $AlPO_4$ was selected as the final formulation for further development. Subjects in the PCV13+$AlPO_4$ group received either 23vPS or PCV13+$AlPO_4$ 12 months after the initial vaccination. Subjects in the non-selected PCV13 (without $AlPO_4$) group received a subsequent dose of 23vPS 12 months after the initial vaccination. Group 3 did not receive any subsequent vaccinations.
[d] This study is ongoing and will also evaluate immune responses to a 2nd dose of PCV13 given 5 years after an initial dose of PCV13.
[e] PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; PCV9 includes the 7 serotypes in PCV7 plus serotypes 1 and 5.
PCV7+PCV9: one vial of commercial PCV7 was used to reconstitute one vial of lyophilized PCV9. The final formulation contains 4 µg of pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F and 8 µg of 6B, 2 µg of serotype 1 and 5, 0.5 mg of $AlPO_4$ (0.125 elemental Al), and 37 µg CRM_{197}. After gently shaking to re-suspend, a single IM 0.5 mL dose was administered to the deltoid muscle.
2xPCV7 + 2xPCV9: Two vials of commercial PCV7 were used to reconstitute two vials of lyophilized PCV9. The final formulation contained 8 µg of pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F, 16 µg 6B, 4 µg of serotypes 1, 5, 0.25 mg aluminum and 76 µg CRM_{197}. After gently shaking to re-suspend, a single IM 1.0 mL dose was administered to the deltoid muscle.
[f] No 6 month follow-up phone contact.
Source: m5.2 Tabular Listing of All Clinical Studies - Adult

5.0 Primary Clinical Immunogenicity Studies

Two studies, 6115A1-004 and 6115A1-3005, comprised the primary studies to demonstrate immunologic non-inferiority (inferred efficacy).

5.1 Study 6115A1-004 (NCT00427895)

Title: A phase 3 randomized, active-controlled, modified double-blind trial evaluating the safety, tolerability, and immunogenicity of PCV13 compared to 23vPS in adults aged 60 to 64 years who are naive to 23vPS and the safety and immunogenicity of PCV13 in adults 18 to 59 years old who are naïve to 23vPS.

5.1.1 Study design

Study 6115A1-004 is a phase 3, multicenter trial with three age cohorts. For cohort 1, a parallel-group, randomized, active-controlled, modified double-blind design was used. For cohort 2, the study was open-label and responses were compared to those of cohort 1. The initial study protocol involved a single study vaccination in all age cohorts. The protocol was amended, adding a second vaccination 3 to 4 years after the initial study vaccination for subjects enrolled in cohorts 1 and 2.

Table 2. Study 6115A1-004 design

Age Cohorts	Population (# planned) N= 2010	Vaccination 1 (Year 0)	Vaccination 2 (Year 3.5)	Blood Draws
1: 60-64 yrs	n= 370	PCV13	PCV13	Pre-dose 1 and 2 1 month post-dose 1 and 2 1 year post-dose 1
			23vPS	
	n= 370	23vPS	23vPS	
2: 50-59 yrs	n= 370	PCV13	PCV13	
3: 18-49 yrs	n= 900[a]	PCV13	N/A	Pre-dose 1 1 month post-vaccination

[a] Cohort 3 subjects were stratified into 3 age subgroups with ~ 300 subjects planned in each subgroup: subgroup 1 (18-29 years), subgroup 2 (30-39 years) and subgroup 3 (40-49 years). Data from cohort 3 were not included in this submission.

Source: 125324/262.0, m5.3.5.1.3, CSR-76149-report body, page 19 and 125324/262.10, m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses.

5.1.2 Vaccination 1 (Year 0) Study objectives

Primary Objectives:

First Cohort: 60-64 Years Old

1. To demonstrate that the immune responses to the 12 common pneumococcal serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by PCV13 are noninferior to the respective immune responses induced by 23vPS, when measured by serotype-specific OPA GMTs one month after vaccination.
2. To demonstrate that the proportion of subjects receiving PCV13 and exhibiting a 4-fold increase in the anti-6A OPA titer one month after vaccination is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting the same 4-fold increase.

Second Cohort: 50-59 Years Old
To demonstrate that the immune responses to the 13 serotypes in PCV13 in the 50-59 year age group (cohort 2) are non-inferior to the corresponding immune response in the 60-64 year age group (cohort 1), as measured by serotype-specific OPA GMTs 1 month after vaccination.

Secondary Objectives:
First Cohort: 60-64 Years Old
1. To demonstrate that, 1 month post-vaccination, the anti-6A OPA GMT in PCV13 recipients is statistically significantly greater than the anti-6A GMT in 23vPS recipients.
2. To demonstrate that PCV13 is statistically significantly more immunogenic than 23vPS for at least some of the 12 common serotypes, as measured by serotype-specific OPA GMTs 1 month after vaccination.

Exploratory Objectives:
First Cohort: 60-64 Years Old
To assess persistence of antibody by OPA GMTs in a subset of 200 subjects (n=100 subjects per vaccine group) 1 year after vaccination.

Second Cohort: 50-59 Years Old
To assess persistence of antibody in the 50-59 year age group by OPA GMTs in a subset of 200 subjects 1 year after vaccination.

5.1.3 Vaccination 2 (Year 3.5) Comparisons of Interest
Descriptive comparisons were made between the vaccine regimens based on GMTs/GMCs and corresponding confidence intervals. Although there were no formal power calculations for vaccination 2 analyses, the same criteria used for immune response comparisons in other adult studies with PCV13 were used to evaluate the immune response to vaccination 2. For OPA GMT comparisons, the 2-fold non-inferiority criterion was achieved if the lower limit (LL) of the 95% CI for the GMT ratio was > 0.5. For within group comparisons of response to vaccination 2 versus vaccination 1, non-inferiority was not claimed, but serotypes showing a 2-fold rise in GMTs (LL of 95% CI > 0.5) were noted. Responses were considered statistically significantly greater if the LL of the 95% CI for the GMT ratio or the GMFR > 1.0. Responses were considered statistically significantly lower if the upper limit of the 95% CI for the GMT ratio or the GMFR was < 1.0.

5.1.4 Populations Analyzed
Two analysis populations were defined for immunogenicity analyses: the evaluable (the primary analysis population) and all-available immunogenicity populations. The vaccination 1 and vaccination 2 all-available populations included all subjects who had at least 1 valid and determinate assay result related to the proposed analysis. For immunogenicity analyses, subjects were analyzed according to their randomized treatment assignment.

The vaccination 1 evaluable immunogenicity population included subjects who:

1. Met study eligibility criteria
2. For those in the 60 to 64 year cohort, were randomized to receive the treatment assignment
3. Were 60 to 64 years old in cohort 1 or 50 to 59 years old in cohort 2 on the day of first vaccination
4. Received the vaccine to which they were randomized or assigned (cohort 1 subjects were randomized to PCV13 or 23vPS and cohort 2 subjects were assigned to PCV13)
5. Had ≥ 1 valid and determinate assay result for antibody response to any pneumococcal serotype
6. Had prevaccination blood drawn on the day of vaccination or within 15 days prior to day 1
7. Had post-vaccination blood drawn within the prescribed time windows. The blood draw time window of 29 to 43 days after vaccination were expanded to 28 to 57 days after vaccination for reporting purposes (in the SAP, the blood draw windows were expanded by 1 extra day before and 14 days after the windows originally specified in the protocol)
8. Received no prohibited vaccines
9. Had no other major protocol violation

The vaccination 2 evaluable immunogenicity population included eligible subjects who:

1. Satisfied eligibility criteria to receive vaccination 2
2. Received vaccination 2 to which they were stratified (cohort 1) or assigned (cohort 2)
3. Received vaccination 1 to which they were randomized (cohort 1) or enrolled (cohort 2)
4. Had at least 1 valid and determinate assay result to any pneumococcal serotypes
5. Had pre-dose 2 blood drawn on the same day as the day of vaccination or within 15 days prior to day 1
6. Had post-dose 2 blood drawn within the prescribed time window (the blood draw windows specified in the protocol (i.e., 29 to 43 days after visit 5) were expanded to 28 to 57 days after visit 5 for reporting purposes
7. Received no prohibited vaccines
8. Had no other major protocol violations as determined by the global clinical project team leader or global medical monitor

5.1.5 Immunogenicity Results

Cohort 1 (60 to 64 years of age): Primary Immunogenicity Objectives

12 Common Serotypes: OPA GMTs One Month Post-vaccination (Table 3)
For the 12 common serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), the criterion for demonstrating non-inferiority of PCV13 compared to 23vPS was a lower limit of the 2-sided 95% CI for the OPA GMT ratio (PCV13/23vPS) exceeding 0.5. This 2-fold criterion was met by each of the 12 serotypes. The lower limit of the GMT ratio exceeded 1.0 for 8 serotypes (1, 4, 6B, 7F, 9V, 18C 19A, and 23F).

Table 3. Study 6115A1-004. Pneumococcal OPA GMTs 1 Month After Vaccination in 23vPS-Naïve Cohort 1 Subjects 60 to 64 Yrs Old (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMT Ratio (PCV13 / 23vPS) and 95% CI	
	PCV13			23vPS				
Serotype	n[a]	GMT	95% CI[b]	n[a]	GMT	95% CI[b]	Ratio[c]	95% CI[d]
1	404	146	124, 173	402	104	88, 124	1.4	1.10, 1.78
3	394	93	81, 107	401	85	74, 98	1.1	0.90, 1.32
4	359	2062	1694, 2511	367	1295	1046, 1603	1.6	1.19, 2.13
5	392	199	164, 242	393	162	134, 198	1.2	0.93, 1.62
6B	371	1984	1604, 2454	371	788	616, 1009	2.5	1.82, 3.48
7F	394	1120	908, 1383	396	405	312, 525	2.8	1.98, 3.87
9V	367	1164	935, 1448	368	407	307, 540	2.9	2.00, 4.08
14	375	612	490, 764	378	692	553, 866	0.9	0.64, 1.21
18C	379	1726	1430, 2083	381	925	735, 1163	1.9	1.39, 2.51
19A	392	682	597, 780	388	352	297, 416	1.9	1.56, 2.41
19F	377	517	421, 635	370	539	442, 658	1.0	0.72, 1.28
23F	375	375	297, 473	375	72	56, 93	5.2	3.67, 7.33
6A	401	2593	2147, 3131	392	213	160, 284	12.1	8.63, 17.08

[a] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[b] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[c] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[d] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13 – 23vPS).
This table presents results from a co-primary study objective and co-secondary objective. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76149-report body, page 59 (Table 9-2) and pages 302-303 (Table 15.20).

Serotype 6A: Proportion of Subjects with a ≥ 4-Fold Increase in OPA Titer [From Day 1 (Prior to Vaccination) to One Month Post-Vaccination] (Table 4)
For serotype 6A, the criterion for demonstrating statistically significantly greater responses following PCV13 compared to 23vPS was a lower limit of the 2-sided 95% CI for the difference in proportions of subjects achieving a 4-fold increase in OPA titer (PCV13 – 23vPS) > 0. This criterion was met by serotype 6A. It was noted that the 49%

of 23vPS recipients achieved a ≥ 4 fold increase in anti-6A OPA titers; this is consistent with functional anti-6A antibody production due to cross-reactivity with serotype 6B.

Table 4. Study 6115A1-004. Proportion of 23vPS-Naive Subjects Aged 60 to 64 Years (Cohort 1) Achieving a ≥ 4-Fold Increase in anti-6A OPA Titer One Month Post-Vaccination (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						Difference in Proportions (PCV13 – 23vPS)	
	PCV13 N[a]=374			23vPS N[a]=377				
Serotype	**n[b]**	**%**	**95% CI[c]**	**n[b]**	**%**	**95% CI[c]**	**Difference (%)**	**95% CI[d]**
6A	331	88.5	84.8, 91.6	186	49.3	44.2, 54.5	39.2	33.0, 45.1

[a] N = Number of subjects with a determinate OPA antibody titer to the specified serotype.
[b] n = Number of subjects with an antibody titer who met the comparison level for the given serotype.
[c] Exact 2-sided CI based upon the observed proportion of subjects.
[d] Exact 2-sided CI for the difference in proportions, expressed as a percentage.
This table presents results from a co-primary study objective. Success criteria were met for demonstrating statistically significantly greater responses when the lower limit of the 2-sided 95% CI for the difference between groups (PCV13 minus 23vPS) was > 0.
Source: 125324/262.0,m5.3.5.1.3, CSR-76149-report body, page 63 (Table 9-5).

Cohort 2 (50 to 59 years of age): Primary Immunogenicity Objectives

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month Post-vaccination (Table 5)
For the 13 pneumococcal serotypes contained in PCV13, the criterion for demonstrating non-inferiority of a single dose of PCV13 in subjects 50-59 years of age (cohort 2) compared to a single dose of PCV13 in subjects 60-64 years of age (cohort 1) was a lower limit of the 2-sided 95% CI for the geometric mean ratio of the OPA GMTs at one month post-vaccination (Cohort 2 / Cohort 1) > 0.5. <u>This 2-fold criterion was met by each of the 13 vaccine serotypes. The lower limit of the GMT ratio exceeded 1.0 for 9 serotypes (1, 4, 5, 6A, 6B, 7F, 9V, 14 and 19A)</u>.

Table 5: Study 6115A1-004. Pneumococcal OPA GMTs One Month After Vaccination in 23vPS-Naïve Subjects in Cohorts 1 and 2 (Evaluable Immunogenicity Population)

	Subjects Randomized/Assigned to PCV13						GMT Ratio and 95% CI (Cohort 2 / Cohort 1)	
	50-59 Years of Age (Cohort 2)			60-64 Years of Age (Cohort 1)				
Serotype	**n[a]**	**GMT**	**95% CI[b]**	**n[a]**	**GMT**	**95% CI[b]**	**Ratio[c]**	**95% CI[d]**
1	382	200	170, 236	404	146	124, 173	1.4	1.08, 1.73
3	379	91	80, 105	394	93	81, 107	1.0	0.81, 1.19
4	350	2833	2412, 3327	359	2062	1694, 2511	1.4	1.07, 1.77
5	373	269	218, 333	392	199	164, 242	1.4	1.01, 1.80
6A	384	4328	3658, 5122	401	2593	2147, 3131	1.7	1.30, 2.15
6B	361	3212	2729, 3781	371	1984	1604, 2454	1.6	1.24, 2.12
7F	378	1520	1275, 1812	394	1120	908, 1383	1.4	1.03, 1.79
9V	364	1726	1429, 2086	367	1164	935, 1448	1.5	1.11, 1.98
14	373	957	780, 1175	375	612	490, 764	1.6	1.16, 2.12
18C	373	1939	1599, 2350	379	1726	1430, 2083	1.1	0.86, 1.47
19A	377	956	838, 1091	392	682	597, 780	1.4	1.16, 1.69
19F	367	599	491, 731	377	517	421, 635	1.2	0.87, 1.54
23F	368	494	387, 631	375	375	297, 473	1.3	0.94, 1.84

[a] n=Number of subjects with a determinate OPA titer to the specified serotype.
[b] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[c] Ratio of GMTs is calculated by back transforming the mean difference between vaccine cohorts on the logarithmic scale.
[d] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (cohort 2 – cohort 1).
This table presents results from a primary study objective. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76149-report body, page 79 (Table 9-9) and pages 67-69 (Table 9-6).

Cohort 1 (60 to 64 yrs): Secondary Immunogenicity Objectives

12 Common Serotypes: OPA GMTs at One Month Post-Vaccination (Table 3)
A secondary objective for cohort 1 was to demonstrate that PCV13 is statistically significantly more immunogenic than 23vPS for at least some of the 12 common serotypes. The success criterion was a lower limit of the 2-sided 95% CI for the GMT ratio (PCV13 / 23vPS) exceeding 1.0. This criterion was met by 8 of the 12 common serotypes (1, 4, 6B, 7F, 9V, 18C, 19A, and 23F).

Serotype 6A: OPA GMT at One Month Post-Vaccination (Table 3)
A co-secondary objective for cohort 1 was to demonstrate that PCV13 was statistically significantly more immunogenic than 23vPS for serotype 6A based on a lower limit of the 2-sided 95% CI for the GMT ratio (PCV13 / 23vPS) exceeding 2.0. This criterion was met by serotype 6A.

Cohort 1 and 2: Exploratory Objective
PCV13 Pneumococcal Serotypes: OPA Antibody Persistence 1 Year After Vaccination (Table 6)
An exploratory objective was to assess the persistence of OPA antibodies 1 year post-vaccination in a subset of subjects (n=100 per vaccine group). In all study subjects, OPA GMTs were higher at 1 month post-vaccination compared to pre-vaccination, lower at 1 year compared to 1 month post-vaccination, and higher at 1 year post-vaccination compared to pre-vaccination (baseline). Subjects in Cohort 2 (50 to 59 years) generally had higher immune responses compared to subjects in cohort 1 (60 to 64 years).

Table 6: Study 6115A1-004. Pneumococcal OPA GMTs in Adults 50 to 64 Years of Age (Evaluable Immunogenicity Population)

Serotype	Time Point	Cohort 1 (60 to 64 Years) Vaccine Group (As Randomized)						Cohort 2 (50 to 59 Years) Vaccine (As Assigned)		
		PCV13			23vPS			PCV13		
		n	GMT	95% CI[b]	n[a]	GMT	95% CI[b]	n[a]	GMT	95% CI[b]
1	Pre-Vaccination	411	5	4.9, 5.7	407	6	5.5, 6.6	384	5	4.8, 5.6
	1 Month Post-Vaccination	404	146	124.0, 172.9	402	104	87.7, 124.4	382	200	170.3, 236.0
	1 Year Post-Vaccination	99	38	27.2, 53.1	98	28	19.7, 38.7	95	54	37.9, 77.2
3	Pre-Vaccination	400	7	6.1, 7.6	401	8	6.7, 8.5	380	7	6.2, 7.9
	1 Month Post-Vaccination	394	93	81.1, 106.6	401	85	74.2, 98.3	379	91	79.9, 104.7
	1 Year Post-Vaccination	97	19	13.9, 25.3	94	17	12.2, 23.2	93	20	15.0, 27.2
4	Pre-Vaccination	354	15	11.5, 19.9	331	16	12.0, 20.5	318	16	12.2, 21.2
	1 Month Post-Vaccination	359	2062	1693.6, 2510.5	367	1295	1045.9, 1603.0	350	2833	2412.1, 3327.4
	1 Year Post-Vaccination	90	248	148.9, 414.4	86	192	107.2, 345.4	83	863	541.8, 1376.1
5	Pre-Vaccination	405	6	5.3, 6.4	402	6	5.5, 6.8	382	6	5.2, 6.3
	1 Month Post-Vaccination	392	199	164.0, 242.3	393	162	133.6, 197.5	373	269	218.1, 332.5
	1 Year Post-Vaccination	100	35	23.0, 52.1	96	41	26.6, 62.2	93	79	51.9, 121.4
6A	Pre-Vaccination	383	14	11.0, 17.1	391	17	13.2, 21.3	364	19	15.1, 24.7
	1 Month Post-Vaccination	401	2593	2146.7, 3131.1	392	213	160.3, 284.3	384	4328	3658.1, 5121.5
	1 Year Post-Vaccination	95	733	480.0, 1120.3	93	89	50.4, 156.1	92	1147	798.1, 1648.8
6B	Pre-Vaccination	354	37	27.4, 49.6	360	29	21.6, 38.3	335	40	29.3, 53.9
	1 Month Post-Vaccination	371	1984	1604.0, 2453.6	371	788	615.9, 1008.5	361	3212	2728.6, 3781.4
	1 Year Post-Vaccination	98	445	267.5, 739.4	89	216	119.8, 389.7	92	1234	863.3, 1764.4
7F	Pre-Vaccination	399	7	6.2, 8.6	386	7	5.9, 8.2	369	7	6.0, 8.5
	1 Month Post-Vaccination	394	1120	907.6, 1382.9	396	405	311.9, 524.7	378	1520	1274.5, 1812.1
	1 Year Post-Vaccination	98	125	72.6, 216.9	99	72	40.9, 126.6	92	296	183.4, 479.2
9V	Pre-Vaccination	356	22	16.4, 28.3	343	20	14.9, 25.9	326	27	20.0, 36.2
	1 Month Post-Vaccination	367	1164	934.8, 1448.3	368	407	307.2, 539.8	364	1726	1428.5, 2086.2
	1 Year Post-Vaccination	93	193	109.0, 340.5	88	176	94.4, 330.0	92	763	486.7, 1196.2
14	Pre-Vaccination	372	28	21.6, 36.0	379	27	20.8, 34.2	355	45	34.3, 59.5
	1 Month Post-Vaccination	375	612	489.6, 764.2	378	692	553.3, 866.2	373	957	779.6, 1174.5
	1 Year Post-Vaccination	99	240	149.7, 385.0	96	338	198.1, 575.6	91	706	456.3, 1093.3
18C	Pre-Vaccination	393	25	19.5, 31.5	383	25	20.0, 32.2	365	22	17.1, 27.7
	1 Month Post-Vaccination	379	1726	1429.7, 2082.9	381	925	735.3, 1162.9	373	1939	1599.2, 2350.2
	1 Year Post-Vaccination	93	477	304.4, 748.5	95	303	182.5, 502.7	93	652	440.1, 965.4
19A	Pre-Vaccination	385	21	17.9, 25.4	384	23	19.6, 27.8	376	30	24.5, 35.6
	1 Month Post-Vaccination	392	682	596.5, 779.9	388	352	297.0, 416.1	377	956	837.6, 1090.7
	1 Year Post-Vaccination	92	138	101.1, 189.7	91	150	106.8, 210.4	94	303	233.8, 392.9
19F	Pre-Vaccination	383	17	13.7, 20.7	379	16	12.7, 19.0	365	18	14.2, 21.8
	1 Month Post-Vaccination	377	517	420.8, 635.3	370	539	442.1, 658.2	367	599	491.0, 731.0
	1 Year Post-Vaccination	94	102	67.2, 153.6	92	173	113.1, 263.3	87	171	107.5, 272.7
23F	Pre-Vaccination	382	8	7.2, 9.9	386	8	6.4, 8.8	359	8	7.1, 10.0
	1 Month Post-Vaccination	375	375	297.2, 472.6	375	72	55.9, 93.4	368	494	386.8, 630.7
	1 Year Post-Vaccination	94	79	47.7, 132.2	93	40	24.7, 63.6	94	143	86.0, 237.8

[a] n = Number of subjects with valid and determinate assay results for the specified serotype at the given visit. Analysis at 1 year post-vaccination 1 was limited to a subset of 100 subjects per vaccine group.
[b] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
Source: 125324/262.0,m5.3.5.1.3, CSR-76149-report body, pages 67-69 (Table 9-6).

Medical Reviewer Note: Per 21 CFR 314.50(d)(5)(v), the applicant provided sub-group analyses of clinical trial data by age and gender. The results suggest that there may be an effect on immune response based on sex, however the studies were not powered to detect this difference. Further studies will be needed for confirmation.

Subsequent Dosing Immunogenicity Comparisons of Interest

Although study 6115A1-004 was not powered for post-vaccination 2 analyses and there were no pre-specified criteria for achieving non-inferiority, the results below include comparisons using criteria defined in the analyses for vaccination 1. These results are descriptive only.

Primary Comparisons of Interest:

12 Common Serotypes: OPA GMTs 1 Month After Vaccination with PCV13/23vPS (given 3.5 years apart) and 23vPS in 60 to 64 Year Old Subjects (Table 7)

Non-inferiority of PCV13/23vPS compared to 23vPS (lower limit (LL) of 95% CI for the GMT ratio > 0.5) was observed for each of the 12 common serotypes. The LL of the 95% CI for the GMT ratio > 1.0 for 9 of the 12 common serotypes.

Table 7. Study 6115A1-004. OPA GMTs For the 12 Common Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/23vPS[a] and 23vPS in 23vPS-Naïve Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Populations)

	Vaccine Group As Randomized						GMT Ratio [(PCV13/23vPS) / 23vPS] and 95% CI	
	PCV13/23vPS[a]			23vPS				
Serotype	n[b]	GMT	95% CI[c]	n[a]	GMT	95% CI[c]	Ratio[d]	95% CI[e]
1	105	398	306, 516	184	116	89,150	3.4	2.3, 5.1
3	107	164	129, 208	184	105	85,129	1.6	1.1, 2.2
4	107	1875	1489, 2361	174	1420	1066, 1891	1.3	0.9, 2.0
5	106	476	356, 636	181	149	111, 201	3.2	2.0, 5.0
6B	104	2670	2013, 3541	174	1088	775, 1528	2.5	1.5, 4.0
7F	105	1895	1471, 2441	181	403	276, 589	4.7	2.8, 8.0
9V	107	1089	699, 1695	167	654	453, 945	1.7	0.9, 3.0
14	105	1268	952, 1690	173	824	613, 1108	1.5	1.0, 2.4
18C	103	2489	1941, 3193	174	1135	816, 1579	2.2	1.4, 3.5
19A	106	966	763, 1224	182	377	296, 480	2.6	1.8, 3.7
19F	99	1653	1302, 2100	170	621	469, 822	2.7	1.8, 4.0
23F	105	299	204, 438	173	86	59, 125	3.5	2.0, 6.1

[a] 23vPS administered 3.5 years after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[e] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/23vPS – 23vPS).
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 7 (Table 4-1).

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month After Vaccination with PCV13/23vPS (given 3.5 years apart) and 23vPS/23vPS (given 3.5 years apart) in 60 to 64 Year Old Subjects (Table 8)

Non-inferiority of PCV13/23vPS compared to 23vPS/23vPS (LL of 95% CI for the GMT ratio > 0.5) was observed for each of the 13 serotypes. The LL exceeded 1.0 for all 13 serotypes.

Table 8. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/23vPS[a] and 23vPS/23vPS[b] in 23vPS-Naïve Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMT Ratio [(PCV13/23vPS) / (23vPS/23vPS)] and 95% CI	
	PCV13/23vPS[a]			23vPS/23vPS[b]				
Serotype	**n[c]**	**GMT**	**95% CI[d]**	**n[c]**	**GMT**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	105	398	306, 516	186	95	75, 121	4.2	2.9, 6.1
3	107	164	129, 208	181	53	43, 64	3.1	2.3, 4.3
4	107	1875	1489, 2361	174	733	555, 968	2.6	1.7, 3.8
5	106	476	356, 636	180	74	54, 100	6.5	4.1, 10.2
6A	104	832	551, 1256	176	123	83,182	6.8	3.7, 12.3
6B	104	2670	2013, 3541	181	916	670, 1252	2.9	1.8, 4.6
7F	105	1895	1471, 2441	182	497	362, 682	3.8	2.4, 6.0
9V	107	1089	699, 1695	177	187	125, 280	5.8	3.1, 10.8
14	105	1268	952, 1690	180	661	516, 849	1.9	1.3, 2.8
18C	103	2489	1941, 3193	180	802	598, 1077	3.1	2.0, 4.8
19A	106	966	763, 1224	184	364	290, 458	2.7	1.9, 3.8
19F	99	1653	1302, 2100	176	374	286, 488	4.4	3.0, 6.6
23F	105	299	204, 438	181	54	38, 77	5.5	3.2, 9.4

[a] 23vPS administered 3.5 years after an initial study dose of PCV13.
[b] 23vPS administered 3.5 years after an initial study of 23vPS.
[c] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/23vPS – 23vPS/23vPS).
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 8 (Table 4-2).

Secondary Comparisons of Interest

PCV13 Pneumococcal Serotypes: OPA GMTs One Month After PCV13/23vPS (given 3 years apart) and PCV13 in 60 to 64 Year Old Subjects (Table 9)
Non-inferiority of PCV13/23vPS compared to PCV13 (LL of 95% CI for the GMFR > 0.5) was observed for 10 of the 13 serotypes. Non-inferiority was not observed for serotypes 4, 6A, and 9V and the upper limit of the 95% CI for the GMFR was < 1.0 for these three serotypes. The LL exceeded 1.0 for 7 serotypes (1, 3, 5, 7F, 14, 19A, and 19F).

Table 9. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/23vPS[a] and PCV13 in 23vPS-Naïve Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMFR [(PCV13/23vPS) / PCV13] and 95% CI	
	PCV13/23vPS[a]			PCV13				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**GMFR[d]**	**95% CI[c]**
1	100	377	288, 492	100	172	123, 240	2.2	1.6, 2.9
3	96	162	124, 210	96	102	77,136	1.6	1.2, 2.0
4	90	1997	1622, 2459	90	2894	2009, 4170	0.7	**0.5**, **0.9**
5	97	445	331, 600	97	239	166, 343	1.9	1.4, 2.5
6A	100	812	530, 1244	100	2884	1979, 4204	0.3	**0.2**, **0.4**
6B	93	2707	1996, 3673	93	2664	1836, 3867	1.0	0.8, 1.3
7F	100	1818	1398, 2364	100	971	598, 1577	1.9	1.3, 2.8
9V	90	909	548, 1507	90	1474	993, 2188	0.6	**0.4**, **0.9**
14	88	1367	1017, 1836	88	655	409, 1048	2.1	1.4, 3.0
18C	96	2503	1932, 3244	96	2136	1501, 3042	1.2	0.9, 1.5
19A	99	976	761, 1252	99	765	590, 993	1.3	1.1, 1.6
19F	93	1670	1303, 2139	93	675	452, 1007	2.5	1.7, 3.6
23F	94	333	225, 495	94	432	272, 685	0.8	0.6, 1.1

[a] 23vPS administered 3.5 years after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] GMFRs [(PCV13/23vPS)/PCV13] were calculated using all subjects with available data from both post-vaccination 1 and post-vaccination 2 blood draws.
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 10 (Table 4-3).

PCV13 Pneumococcal Serotypes: OPA GMTs One Month After 23vPS/23vPS (given 3.5 years apart) and 23vPS in 60 to 64 Year Old Subjects (Table 10)
Non-inferiority of 23vPS/23vPS compared to 23vPS (LL of 95% CI for the GMFR > 0.5) was observed for 7 serotypes. Non-inferiority was not observed for serotypes 3, 4, 5, 6B, 9V, and 23F. The upper limit of the 95% CI for the GMFR was < 1.0 for 9 serotypes (3, 4, 5, 6A, 9V, 14, 18C, 19F, and 23F).

Table 10. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With 23vPS/23vPS[a] and 23vPS in 23vPS-Naïve Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMFR [(23vPS/23vPS) / 23vPS] and 95% CI	
	23vPS/23vPS[a]			23vPS				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**GMFR[d]**	**95% CI[c]**
1	181	95	75, 122	181	115	88, 149	0.8	0.68, 1.02
3	177	53	43, 65	177	103	84, 128	0.5	**0.44**, **0.59**
4	162	725	543, 968	162	1437	1069, 1933	0.5	**0.40**, **0.64**
5	173	71	52, 97	173	152	112, 206	0.5	**0.39**, **0.56**
6A	167	133	89,198	167	286	184, 446	0.5	**0.35**, **0.62**
6B	168	915	659, 1272	168	1133	804, 1599	0.8	0.62, 1.04
7F	174	466	336, 645	174	440	302, 643	1.1	0.81, 1.37
9V	157	181	118, 277	157	669	458, 978	0.3	**0.18**, **0.41**
14	165	619	474, 809	165	823	608, 1113	0.8	0.60, **0.95**
18C	165	822	602, 1124	165	1096	778, 1544	0.8	0.60, **0.94**
19A	177	361	287, 454	177	374	292, 478	1.0	0.83, 1.12
19F	158	405	307, 533	158	596	447, 795	0.7	0.57, **0.81**
23F	165	56	39, 81	165	91	62, 134	0.6	**0.50**, **0.76**

[a] 23vPS administered 3.5 years after an initial study dose of 23vPS.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] GMFRs [(23vPS/23vPS)/23vPS] were calculated using all subjects with available data from both post-vaccination 1 and post-vaccination 2 blood draws.
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 11 (Table 4-4).

PCV13 Pneumococcal Serotypes: OPA GMTs One Month After PCV13/PCV13 (given 3.5 years apart) and PCV13 in 60 to 64 Year Old Subjects (Table 11)
Non-inferiority of PCV13/PCV13 compared to PCV13 (LL of 95% CI for the GMFR > 0.5) was observed for 11 of 13 serotypes. The LL was 0.5 for serotypes 4 and 9V. The LL was > 1.0 for 7 of 13 serotypes (1, 5, 6B, 14, 19A, 19F, and 23F).

Table 11. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/PCV13[a] and PCV13 in Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMFR [(PCV13/PCV13) / PCV13] and 95% CI	
	PCV13/PCV13[a]			PCV13				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**GMFR[d]**	**95% CI[c]**
1	102	334	253, 442	102	155	113, 214	2.2	1.6, 2.9
3	99	87	69, 111	99	102	78, 134	0.9	0.7, 1.1
4	92	1194	894, 1594	92	1626	1101, 2403	0.7	**0.5**, 1.0
5	97	277	196, 391	97	180	122, 266	1.5	1.1, 2.2
6A	99	2126	1492, 3031	99	2411	1617, 3595	0.9	0.6, 1.2
6B	95	4357	3402, 5581	95	2312	1593, 3357	1.9	1.4, 2.5
7F	100	1226	970, 1549	100	928	603, 1427	1.3	0.9, 2.0
9V	94	855	562, 1304	94	1163	764, 1771	0.7	**0.5**, 1.2
14	98	1040	809, 1336	98	746	510, 1090	1.4	1.0, 1.9
18C	92	1837	1381, 2444	92	1529	1030, 2272	1.2	0.9, 1.6
19A	102	791	619, 1011	102	591	442, 790	1.3	1.1, 1.7
19F	94	989	708, 1381	94	467	305, 715	2.1	1.5, 3.0
23F	97	918	646, 1305	97	448	290, 692	2.1	1.4, 3.0

[a] PCV13 administered 3.5 years after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] GMFRs [(PCV13/PCV13)/PCV13] were calculated using all subjects with available data from both post-vaccination 1 and post-vaccination 2 blood draws.
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 12 (Table 4-5).

PCV13 Pneumococcal Serotypes: OPA GMTs One Month After PCV13/PCV13 (given 3.5 years apart) and PCV13 in 50 5o 59 Year Old Subjects (Table 12)
Non-inferiority of PCV13/PCV13 compared to PCV13 (LL of 95% CI for the GMFR > 0.5) was observed for 12 of 13 serotypes. The LL was 0.5 for serotype 4. The LL was > 1.0 for 5 serotypes (1, 6B, 14, 19F, and 23F). The upper limit was < 1.0 for 2 serotypes (4 and 6A).

Table 12. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/PCV13[a] and PCV13 in Subjects Aged 50 to 59 Years (Cohort 2) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMFR [(PCV13/PCV13) / PCV13] and 95% CI	
	PCV13/PCV13[a]			PCV13				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**GMFR[d]**	**95% CI[c]**
1	202	296	245, 358	202	198	158, 248	1.5	1.2, 1.9
3	199	85	73, 99	199	91	76, 110	0.9	0.8, 1.1
4	181	1685	1468, 1935	181	2817	2272, 3492	0.6	**0.5**, **0.7**
5	194	291	230, 369	194	235	174, 317	1.2	1.0, 1.5
6A	202	3143	2593, 3810	202	4347	3454, 5471	0.7	0.6, **0.9**
6B	189	4886	4209, 5671	189	3085	2410, 3949	1.6	1.3, 2.0
7F	199	1659	1450, 1898	199	1596	1274, 1999	1.0	0.8, 1.3
9V	193	1492	1229, 1811	193	1933	1513, 2471	0.8	0.6, 1.0
14	193	1278	1083, 1509	193	865	650, 1152	1.5	1.2, 1.9
18C	192	2156	1833, 2536	192	1742	1320, 2299	1.2	1.0, 1.6
19A	200	1048	905, 1214	200	959	807, 1140	1.1	0.9, 1.3
19F	189	1182	989, 1413	189	633	492, 814	1.9	1.5, 2.3
23F	189	1188	949, 1486	189	563	404, 783	2.1	1.6, 2.7

[a] PCV13 administered 3.5 years after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] GMFRs [(PCV13/PCV13)/PCV13] were calculated using all subjects with available data from both post-vaccination 1 and post-vaccination 2 blood draws.
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 13 (Table 4-6).

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month After Vaccination with PCV13/PCV13 (given 3.5 years apart) in 60 to 64 Year Old Subjects versus 50 to 59 Year Old Subjects (Table 13)

Non-inferiority of PCV13/PCV13 given to 60 to 64 year old adults compared to PCV13/PCV13 given to 50 to 59 year old adults (LL of 95% CI for the GMT ratio > 0.5) was observed for 10 of the 13 serotypes. Non-inferiority was not observed for serotypes 6A, 9V, and 23F. The upper limit was < 1.0 for serotypes 4, 6A, 7F, 9V and 19A.

Table 13. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/PCV13[a] in Subjects Aged 60 to 64 Years (Cohort 1) Versus Subjects Aged 50 to 59 Years (Cohort 2) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMT Ratio (Cohort 1 / Cohort 2) and 95% CI	
	60 to 64 Yr Olds (Cohort 1) PCV13/PCV13[a]			50 to 59 Yr Olds (Cohort 2) PCV13/PCV13[a]				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**Ratio[d]**	**95% CI[e]**
1	103	334	253, 440	205	292	241, 355	1.1	0.82, 1.59
3	102	87	68, 110	203	83	71, 97	1.0	0.79, 1.37
4	103	1175	883, 1563	200	1657	1444, 1901	0.7	0.54, **0.94**
5	102	276	198, 386	203	293	233, 369	0.9	0.63, 1.41
6A	103	2064	1466, 2908	205	3104	2565, 3757	0.7	**0.46**, **0.95**
6B	104	4184	3309, 5291	202	4885	4164, 5731	0.9	0.65, 1.13
7F	102	1223	971, 1541	204	1654	1449, 1889	0.7	0.58, **0.95**
9V	103	770	503, 1181	202	1421	1169, 1728	0.5	**0.36**, **0.81**
14	104	1031	814, 1306	203	1186	992, 1416	0.9	0.64, 1.17
18C	100	1918	1459, 2521	199	2066	1742, 2450	0.9	0.68, 1.26
19A	104	789	620, 1003	205	1039	898, 1202	0.8	0.58, **0.99**
19F	101	958	700, 1313	196	1171	982, 1397	0.8	0.59, 1.14
23F	101	867	606, 1239)	201	1158	929, 1443	0.7	**0.50**, 1.12

[a] PCV13 administered 3.5 years after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[e] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (Cohort 1 – Cohort 2).
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 14 (Table 4-7).

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month After Vaccination with PCV13/PCV13 (given 3. 5 years apart) and PCV13/23vPS (given 3.5 years apart) in 60 to 64 Year Old Subjects (Table 14)

Non-inferiority of PCV13/PCV13 compared to PCV13/23vPS (LL of 95% CI for the GMT ratio > 0.5) was observed for 7 of 13 serotypes. Non-inferiority was not observed for serotypes 3, 4, 5, 7F, 9V, and 19F. The LL exceeded 1.0 for serotypes 6A, 6B and 23F. The upper limit was < 1.0 for 5 serotypes (3, 4, 5, 7F, and 19F).

Table 14. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/PCV13[a] and PCV13/23vPS[b] in Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMT Ratio [(PCV13/PCV13) / (PCV13/23vPS) and 95% CI	
	PCV13/PCV13[a]			PCV13/23vPS[b]				
Serotype	**n[c]**	**GMT**	**95% CI[c]**	**n[c]**	**GMT**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	103	334	253, 440	105	398	306, 516	0.8	0.58, 1.22
3	102	87	68, 110	107	164	129, 208	0.5	**0.38**, **0.74**
4	103	1175	883, 1563	107	1875	1489, 2361	0.6	**0.44**, **0.90**
5	102	276	198, 386	106	476	356, 636	0.6	**0.37**, **0.90**
6A	103	2064	1466, 2908	104	832	551, 1256	2.5	1.46, 4.23
6B	104	4184	3309, 5291	104	2670	2013, 3541	1.6	1.09, 2.26
7F	102	1223	971, 1541	105	1895	1471, 2441	0.6	**0.46**, **0.91**
9V	103	770	503, 1181	107	1089	699, 1695	0.7	**0.38**, 1.31
14	104	1031	814, 1306	105	1268	952, 1690	0.8	0.56, 1.18
18C	100	1918	1459, 2521	103	2489	1941, 3193	0.8	0.53, 1.11
19A	104	789	620, 1003	106	966	763, 1224	0.8	0.58, 1.14
19F	101	958	700, 1313	99	1653	1302, 2100	0.6	**0.39**, **0.86**
23F	101	867	606, 1239	105	299	204, 438	2.9	1.72, 4.88

[a] PCV13 administered 3.5 years after an initial study dose of PCV13.
[b] 23vPS administered 3.5 years after an initial study dose of PCV13.
[c] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/PCV13 – PCV13/23vPS).
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 15 (Table 4-8).

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month After Vaccination with PCV13/PCV13 (given 3.5 years apart) and 23vPS/23vPS (given 3.5 years apart) in 60 to 64 Year Old Subjects (Table 15)

Non-inferiority of PCV13/PCV13 compared to 23vPS/23vPS (LL of 95% CI for the GMT ratio > 0.5) was observed for each of the 13 serotypes. The LL exceeded 1.0 for all serotypes.

Table 15. Study 6115A1-004. OPA GMTs For the PCV13 Pneumococcal Serotypes Measured 1 Month After Vaccination With PCV13/PCV13[a] and 23vPS/23vPS[b] in Subjects Aged 60 to 64 Years (Cohort 1) (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMT Ratio [(PCV13/PCV13) / (23vPS/23vPS) and 95% CI	
	PCV13/PCV13[a]			23vPS/23vPS[b]				
Serotype	**n[c]**	**GMT**	**95% CI[d]**	**n[c]**	**GMT**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	103	334	253, 440	186	95	75, 121	3.5	2.4, 5.1
3	102	87	68, 110	181	53	43, 64	1.6	1.2, 2.3
4	103	1175	883, 1563	174	733	555, 968	1.6	1.1, 2.4
5	102	276	198, 386	180	74	54, 100	3.7	2.3, 6.0
6A	103	2064	1466, 2908	176	123	82.9, 182	16.8	9.5, 29.9
6B	104	4184	3309, 5291	181	916	670, 1252	4.6	2.9, 7.2
7F	102	1223	971, 1541	182	497	362, 682	2.5	1.6, 3.9
9V	103	770	503, 1181	177	187	125, 280	4.1	2.2, 7.7
14	104	1031	814, 1306	180	661	516, 849	1.6	1.1, 2.3
18C	100	1918	1459, 2521	180	802	598, 1077	2.4	1.5, 3.7
19A	104	789	620, 1003	184	364	290, 458	2.2	1.5, 3.1
19F	101	958	700, 1313	176	374	286, 488	2.6	1.7, 3.9
23F	101	867	606, 1239	181	54	38, 77	15.9	9.3, 27.2

[a] PCV13 administered 3.5 years after an initial study dose of PCV13.
[b] 23vPS administered 3.5 years after an initial study dose of 23vPS.
[c] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/PCV13 – 23vPS/23vPS).
This table represents descriptive data.
Source: 125324/262.10,m1.11.3, Efficacy Information Amendment, Summary of 004 Extension OPA Analyses, page 16 (Table 4-9).

5.2 Study 6115A1-3005 (NCT00546572)

Title: A phase 3, randomized, active-controlled, modified double-blind trial evaluating the safety, tolerability, and immunogenicity of Prevnar 13 compared with a 23-valent pneumococcal polysaccharide vaccine (23vPS) in ambulatory elderly individuals aged 70 years and older who received 1 dose of 23vPS at least 5 years before study enrollment.

5.2.1 Study design

Study 6115A1-3005 is a phase 3, multicenter trial. At year 0, the study was a randomized (1:1), active-controlled, modified double-blind trial. At year 1, all subjects received PCV13.

Table 16. Study 6115A1-3005 design:

Pre-immunized Subjects	Group	N (enrolled)	N (evaluable)	Vaccination	
				Year 0	Year 1
Adults aged ≥ 70 years who received prior 23vPS vaccination ≥ 5 years ago	1	462	406	PCV13	PCV13
	2	462	406	23vPS	PCV13

Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page 19.

5.2.2 Study objectives

Primary objectives

1. To demonstrate that PCV13 is as immunogenic as 23vPS for the 12 common serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) contained in PCV13 and 23vPS, as measured by serotype-specific OPA GMTs 1 month after initial study vaccination (year 0).

2. To demonstrate that the proportion of subjects receiving PCV13 and exhibiting a 4-fold rise in the 6A OPA titer is statistically significantly greater than the proportion of subjects receiving 23vPS exhibiting a 4-fold rise, measured 1 month after initial study vaccination (year 0).

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

Secondary objectives

Secondary Objectives at Year 0:

1. To demonstrate that PCV13 is statistically significantly more immunogenic than 23vPS for at least some of the 12 common serotypes, as measured by serotype-specific OPA GMTs 1 month after initial study vaccination.

2. To demonstrate that the anti-6A OPA GMT in the PCV13 recipients is statistically significantly greater than the anti-6A titer in 23vPS recipients measured 1 month after initial study vaccination.

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

Secondary Objectives at Year 1:

1. To demonstrate that the immune response to a second dose of PCV13 administered 1 year after an initial study dose of PCV13 is noninferior to the immune response to the initial study dose of PCV13 as measured by serotype-specific OPA GMTs obtained 1 month after study vaccination.

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

2. To demonstrate that the immune response to a second dose of PCV13 administered 1 year after an initial study dose of PCV13 is noninferior to the immune response to 23vPS for the 12 common serotypes, as measured by serotype-specific OPA GMTs obtained 1 month after study vaccination.

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

3. To demonstrate that the anti-6A GMT in recipients of a second dose of PCV13 administered 1 year after the initial study dose of PCV13 is statistically significantly greater than the anti-6A GMT in recipients of an initial study dose of 23vPS (year 0) measured 1 month after study vaccination.

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

Exploratory objectives

Exploratory objectives at year 1:

1. To demonstrate that the immune response to a second dose of PCV13 administered 1 year after the initial study dose of PCV13 is statistically significantly greater than the immune response to an initial study dose of PCV13 administered 1 year after the study dose of 23vPS, as measured by serotype-specific OPA GMTs obtained 1 month after study vaccination.

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

2. To evaluate the immune response to a dose of PCV13 administered 1 year after the study dose of 23vPS relative to the immune response to an initial study dose of PCV13, as measured by serotype-specific OPA GMTs obtained 1 month after study vaccination.

Group	Vaccination	
	Year 0	Year 1
1	PCV13	PCV13
2	23vPS	PCV13

3. To assess antibody titers 1 year after initial study vaccination as measured by serotype-specific OPA GMTs obtained before year 1 study vaccination.

Clinical Reviewer Note: There was no objective in this study to compare the immune response to PCV13 when administered one year after an initial dose of 23vPS to the immune response after an initial dose of 23vPS. This comparison, however, was made in study 3010 (Table 31, page 60).

5.2.3 Populations Analyzed

Two analysis populations were defined for immunogenicity analyses for each vaccination: the evaluable (the primary population) and all-available immunogenicity populations. The all-available population for each vaccination included all subjects who had at least 1 valid and determinate assay result related to that vaccination. For immunogenicity analyses, subjects were analyzed according to their randomized treatment assignment.

The vaccination 1 evaluable immunogenicity population included subjects who:

1. Met study eligibility criteria
2. Were randomly assigned
3. Were 70 years of age or older on the day of first vaccination
4. Received vaccination 1 to which they were randomized assigned
5. Had prevaccination blood drawn on the same day as the day of vaccination 1 or within 15 days before day 1
6. Had postvaccination blood drawn within the required time window. The window specified in the protocol was expanded by 1 day before and 14 days after vaccination (i.e. from days 29 to 43 after visit 1 to days 28 to 57 after visit 1).
7. Had at least 1 valid and determinate assay result for antibody response to any pneumococcal serotype
8. Received no prohibited vaccinations after study dose 1 and before the post-dose 1 blood draw
9. Had no other major protocol violations

The vaccination 2 evaluable immunogenicity population included subjects who:

1. Met study eligibility criteria
2. Were 70 years of age or older on the day of first vaccination
3. Received the study vaccine to which they were randomly assigned at vaccination 1
4. Received PCV13 vaccine at study dose 2
5. Had prevaccination blood drawn on the same day as the day of vaccination 1 or within 15 days before day 1
6. Had pre-vaccination blood drawn on the same day as the day of study dose 2 (351 to 379 days after visit 1) or within 15 days before study dose 2.
7. Had post-vaccination blood drawn within the required time window. The blood draw window specified in the protocol was expanded by 1 extra day before and 14 days after vaccination (i.e. expanded from days 29 to 43 after visit 4 to days 28 to 57 after visit 4).
8. Had at least 1 valid and determinate assay result for antibody response to any pneumococcal serotype
9. Received no prohibited vaccinations after study dose 2 and before the post-dose 2 blood draw
10. Had no other major protocol violations

5.2.4 Immunogenicity Results

Primary Objectives

12 Common Serotypes: OPA GMTs 1 Month After Year 0 Vaccination (Table 17)
For the 12 common serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), the criterion for demonstrating non-inferiority of PCV13 compared to 23vPS was a lower limit of the 2-sided 95% CI for the GMT ratio (PCV13 / 23vPS) exceeding 0.5. This 2-fold criterion was met for each of the 12 common serotypes. The lower limit of the GMT ratio was > 1.0 for 10 serotypes (1, 4, 5, 6B, 7F, 9V, 18C, 19A, 19F, and 3F).

Table 17. Study 6115A1-3005. Pneumococcal OPA GMTs 1 Month After Vaccination at Year 0 in Subjects Aged ≥ 70 Years Who Received 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Vaccination 1 Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						GMT Ratio (PCV13 / 23vPS) and 95% CI	
	PCV13			23vPS				
Serotype	n[a]	GMT	95% CI[b]	n[a]	GMT	95% CI[b]	Ratio[c]	95% CI[d]
1	426	81	68, 96	445	55	46, 65	1.5	1.17 , 1.88
3	405	55	48, 63	424	49	43, 57	1.1	0.91 , 1.35
4	400	545	442, 672	395	203	157, 262	2.7	1.93 , 3.74
5	422	72	60, 87	442	36	30, 43	2.0	1.55 , 2.63
6B	411	1261	1025, 1553	411	417	331, 527	3.0	2.21 , 4.13
7F	420	245	192, 312	431	160	124, 208	1.5	1.07 , 2.18
9V	402	181	138, 237	402	90	68, 120	2.0	1.36 , 2.97
14	411	280	228, 346	410	285	229, 354	1.0	0.73 , 1.33
18C	411	907	762, 1080	416	481	385, 601	1.9	1.42 , 2.50
19A	420	354	308, 408	442	200	170, 234	1.8	1.43 , 2.20
19F	414	333	273, 405	417	214	174, 263	1.6	1.17 , 2.06
23F	403	158	126, 199	417	43	34, 54	3.7	2.69 , 5.09
6A	421	903	727, 1121	433	94	74, 119	9.6	7.00 , 13.26

[a] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[b] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[c] Ratio of GMTs calculated by back transforming the mean difference between vaccine groups on logarithmic scale.
[d] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13 – 23vPS).
This table presents results from co-primary and co-secondary study objectives. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page 62 (Table 9-3).

Serotype 6A: Proportion of Subjects with a 4-Fold Increase in OPA Titer From Before Study Dose 1 to 1 Month After Study Dose 1 (Table 18)
For serotype 6A, the criterion for demonstrating non-inferiority of PCV13 compared to 23vPS was based on a lower limit of the 2-sided 95% CI for the difference in proportions of subjects achieving a 4-fold increase in OPA titer (PCV13 – 23vPS) > 0.0. This criterion was met. It was noted that the approximately 27% of 23vPS recipients achieved a ≥ 4 fold increase in anti-6A OPA titers; this is consistent with functional anti-6A antibody production due to cross-reactivity with serotype 6B. In Table 17, it is noted that the OPA GMT levels are lower among 23vPS recipients compared to PCV13 recipients.

Table 18. Study 6115A1-3005. Comparison of Subjects Achieving a ≥ 4-Fold Increase in OPA Titer for Serotype 6A One Month After Vaccination with PCV13 and 23vPS (Year 0), Subjects Aged ≥ 70 Years and Previously Immunized with 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Vaccination 1 Evaluable Immunogenicity Population)

	Vaccine Group As Randomized						Difference in Proportions (PCV13 – 23vPS)	
	PCV13 N[a]=408			23vPS N[a]=411				
Serotype	**n[b]**	**%**	**95% CI[c]**	**n[b]**	**%**	**95% CI[c]**	**Difference (%)**	**95% CI[d]**
6A	290	71.1	66.4, 75.4	112	27.3	23.0, 31.8	43.8	37.4, 49.9

[a] N = Number of subjects with a determinate OPA antibody titer to the specified serotype.
[b] n = Number of subjects with an antibody titer who met the comparison level for the given serotype.
[c] Exact 2-sided CI based upon the observed proportion of subjects.
[d] Exact 2-sided CI for the difference in proportions, expressed as a percentage.
This table presents results from a co-primary study objective. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the difference between groups (PCV13 – 23vPS) was > 0.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page 65 (Table 9-5).

Secondary Objectives

Secondary Objectives at Year 0

12 Common Serotypes: OPA GMTs One Month After Initial Vaccination (Year 0) (Table 17)
A secondary objective of the study was to demonstrate that based on OPA titers measured 1 month after initial vaccination, PCV13 is statistically significantly more immunogenic than 23vPS for at least some of the 12 common serotypes. The criterion for demonstrating that PCV13 was statistically significantly more immunogenic than 23vPS was based on a lower limit of the 2-sided 95% CI for the GMT ratio (PCV13/23vPS) > 1.0. This criterion was met for 10 of the 12 common serotypes (1, 4, 5, 6B, 7F, 9V, 18C, 19A, 19F, and 23F).

Serotype 6A: OPA GMTs One Month After Initial Vaccination (Year 0) (Table 17)
A secondary objective of the study was to demonstrate that, based on OPA GMTs measured 1 month after initial vaccination, PCV13 was statistically significantly more immunogenic than 23vPS for serotype 6A. The criterion for demonstrating statistical significance was a lower limit of the 2-sided 95% CI for the GMT ratio (PCV13 / 23vPS) > 2.0. This criterion was met; the lower limit of the 95% CI was 7.0.

Secondary Objectives at Year 1

PCV13 Pneumococcal Serotypes: PCV13/PCV13 (given 1 year apart) Compared to an initial dose of PCV13 (Yr 0) (Table 19)

Non-inferiority was achieved for a second dose of PCV13 administered 1 year after an initial study dose of PCV13 compared to an initial dose of PCV13 for each of the 13 Prevnar 13 serotypes (i.e., the lower limit of the 2-sided 95% CI for the OPA GMFR was > 0.5 for each of the 13 serotypes). Statistically significantly greater OPA GMTs were achieved after PCV13/PCV13 compared to PCV13 for serotypes 6A, 6B, and 23F (i.e., the lower limit of the 95% CI was > 1.0 for these 3 serotypes). Statistically significantly lower OPA GMTs were achieved after PCV13/PCV13 compared to PCV13 for serotypes 4 and 5 (i.e.,the upper limit of the 95% CI for the GMFR was < 1.0).

Table 19. Study 6115A1-3005. Pneumococcal OPA GMTs 1 Month After PCV13/PCV13[a] Relative to PCV13 (Yr 0) in Subjects Aged ≥ 70 Years Who Received 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Evaluable Immunogenicity Population)

	PCV13/PCV13[a] (As Randomized)						GMFR [(PCV13/PCV13) / PCV13]		
	Vaccination 1 (Year 0)			Vaccination 2 (Year 1)					
Serotype	**n[b]**	**GMT[c]**	**95% CI[d]**	**n[b]**	**GMT[c]**	**95% CI[d]**	**n[b]**	**GMFR[e]**	**95% CI[d]**
1	361	79	65, 95	361	76	65, 90	361	1.0	0.85, 1.10
3	337	55	47, 64	337	55	48, 63	337	1.0	0.91, 1.11
4	324	614	490, 769	324	487	394, 603	324	0.8	0.68, **0.92**
5	355	69	56, 84	355	57	47, 69	355	0.8	0.73, **0.94**
6A	354	971	771, 1222	354	1169	974, 1403	354	1.2	1.03, 1.40
6B	339	1358	1085, 1700	339	1590	1317, 1920	339	1.2	1.02, 1.35
7F	351	222	170, 290	351	180	138, 234	351	0.8	0.65, 1.01
9V	331	187	139, 250	331	166	124, 221	331	0.9	0.69, 1.15
14	348	265	210, 334	348	241	194, 299	348	0.9	0.79, 1.05
18C	342	918	763, 1104	342	1003	850, 1182	342	1.1	0.97, 1.23
19A	349	349	300, 406	349	341	297, 391	349	1.0	0.89, 1.07
19F	340	329	266, 409	340	322	266, 390	340	1.0	0.83, 1.15
23F	335	167	131, 213	335	309	252, 380	335	1.9	1.60, 2.14

[a] PCV13 administered 1 year after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype at both the post-vaccination 1 and post-vaccination 2 blood draws.
[c] GMTs calculated using all subjects with available data from both the post-vaccination 1 and post-vaccination 2 blood draws.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Geometric mean fold rises (GMFRs) [(PCV13/PCV13) / PCV13] were calculated using all subjects with available data from both the post-vaccination 1 and post-vaccination 2 blood draws.
This table presents results from a co-secondary study objective. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMFR was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page 69 (Table 9-6).

12 Common Serotypes: PCV13/PCV13 (given 1 year apart) compared to an initial dose of 23vPS (Table 20)

For the 12 common serotypes, the criterion to demonstrate that the immune response to a second dose of PCV13 administered 1 year after an initial study dose of PCV13 was non-inferior to the immune response after the initial dose of 23vPS was based on a lower limit of the 2-sided 95% CI for the GMT ratio > 0.5. This criterion was met for each of the 12 common serotypes. The lower limit of the 95% CI was > 1.0 for 9 of 12 common serotypes (1, 4, 5, 6B, 9V, 18C, 19A, 19F, and 23F).

Table 20. Study 6115A1-3005. Pneumococcal OPA GMTs 1 Month After Vaccination, PCV13/PCV13[a] Relative to 23vPS (Yr 0) in Subjects Aged ≥ 70 Years Who Received 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Evaluable Immunogenicity Population)

	Vaccine Sequence (As Randomized)						GMT Ratio [(PCV13/PCV13) / 23vPS] and 95% CI	
	PCV13/PCV13[a]			23vPS				
Serotype	**n[b]**	**GMT[c]**	**95% CI[d]**	**n[b]**	**GMT[c]**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	370	76	65, 90	445	55	46, 65	1.4	1.10 , 1.76
3	362	55	48, 62	424	49	43, 57	1.1	0.91 , 1.34
4	347	472	384, 580	395	203	157, 262	2.3	1.66 , 3.25
5	365	56	47, 68	442	36	30, 43	1.6	1.21 , 2.06
6B	356	1565	1306, 1876	411	417	331, 527	3.8	2.78 , 5.07
7F	365	185	143, 240	431	160	124, 208	1.2	0.80 , 1.67
9V	356	158	120, 210	402	90	68, 120	1.8	1.18 , 2.62
14	366	238	192, 294	410	285	229, 354	0.8	0.62 , 1.13
18C	361	975	829, 1147	416	481	385, 601	2.0	1.53 , 2.69
19A	362	339	296, 387	442	200	170, 234	1.7	1.37 , 2.10
19F	354	311	257, 376	417	214	174, 263	1.5	1.09 , 1.93
23F	360	310	254, 378	417	43	34, 54	7.3	5.36 , 9.82
6A	366	1134	944, 1364	433	94	74, 119	12.1	8.92 , 16.44

[a] PCV13 administered one year after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] GMTs were calculated using all subjects with available data for both the specified blood draws.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs calculated by back transforming the mean difference between vaccine groups on logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/PCV13 – 23vPS).
This table presents results from co-secondary study objectives. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page 702 (Table 9-7).

Serotype 6A: PCV13/PCV13 (given 1 year apart) compared to an initial dose of 23vPS (Table 20)

For serotype 6A, the criterion to demonstrate that the anti-6A immune response to a second dose of PCV13 administered 1 year after an initial dose of PCV13 was statistically significantly greater than the anti-6A immune response after the initial dose of 23vPS was based on a lower limit of the 2-sided 95% CI for the GMT ratio > 2.0. This criterion was met; the lower limit of the 2-sided 95% CI for serotype 6A was 8.92.

Exploratory Objectives at Year 1

12 common serotypes: PCV13/PCV13 (given 1 year apart) relative to 23vPS/PCV13 (given 1 year apart) (Table 21)

The lower limit of the 2-sided 95% CI for the GMT ratio was observed to be greater than 1 for 11 of the 12 common serotypes (all serotypes except serotype 14). This suggests that the OPA titers following PCV13/PCV13 are statistically significantly greater than OPA titers after 23vPS/PCV13. The lower limit of the 95% CI for the GMT ratio was > 0.5 for serotype 14, suggesting non-inferiority of PCV13/PCV13 compared to 23vPS/PCV13 for serotype 14.

Table 21. Study 6115A1-3005. Pneumococcal OPA GMTs 1 Month After PCV13/PCV13[a] Relative to 23vPS/PCV13[b] in Subjects Aged ≥ 70 Years Who Received 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Evaluable Immunogenicity Population)

	Vaccine Sequence (As Randomized)						GMT Ratio (PCV13/PCV13 to 23vPS/PCV13) and 95% CI	
	PCV13/PCV13[a]			23vPS/PCV13[b]				
Serotype	n[c]	GMT[d]	95% CI[e]	n[c]	GMT[d]	95% CI[e]	Ratio[f]	95% CI[g]
1	370	76	65, 90	367	34	29, 41	2.2	1.74 , 2.82
3	362	55	48, 62	362	33	28, 38	1.7	1.36 , 2.03
4	347	472	384, 580	338	267	210, 340	1.8	1.29 , 2.42
5	365	56	47, 68	362	42	34, 51	1.4	1.03 , 1.79
6B	356	1565	1306, 1876	352	721	566, 919	2.2	1.61 , 2.94
7F	365	185	143, 240	357	120	91, 159	1.5	1.05 , 2.24
9V	356	158	120, 210	349	72	53, 96	2.2	1.47 , 3.32
14	366	238	192, 294	361	194	154, 245	1.2	0.89 , 1.68
18C	361	975	829, 1147	360	513	413, 637	1.9	1.45 , 2.49
19A	362	339	296, 387	362	248	211, 291	1.4	1.11 , 1.68
19F	354	311	257, 376	358	180	145, 224	1.7	1.30 , 2.30
23F	360	310	254, 378	349	87	67, 113	3.6	2.57 , 4.93
6A	366	1134	944, 1364	352	549	437, 690	2.1	1.54 , 2.77

[a] PCV13 administered one year after an initial study dose of PCV13.
[b] PCV13 administered one year after an initial study dose of 23vPS.
[c] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[d] GMTs were calculated using all subjects with available data for both the specified blood draws.
[e] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[f] Ratio of GMTs is calculated by back transforming the mean difference between vaccine sequence on the logarithmic scale.
[g] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/PCV13 – 23vPS/PCV13).
This table represents descriptive results from an exploratory study objective.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page 71 (Table 9-8).

13 Vaccine Serotypes: 23vPS/PCV13 (given 1 year apart) compared to an initial study dose of PCV13 (Table 22)

The lower limit of the 2-sided 95% CI for the GMT ratio was observed to be greater than 1 for none of the 13 serotypes contained in PCV13. In addition, the upper limit of the 2-sided 95% CI was less than 1. This suggests that the OPA titers following 23vPS/PCV13 are statistically significantly lower compared to PCV13 for all 13 serotypes contained in PCV13. The lower limit of the 95% CI was observed to be less than 0.5 for 11 of the 13 vaccine serotypes (all serotypes except 14 and 19A), suggesting the lack of non-inferiority of 23vPS/PCV13 compared to PCV13.

Table 22. Study 6115A1-3005. Pneumococcal OPA GMTs 1 Month After 23vPS/PCV13[a] Relative to an Initial Dose of PCV13 in Subjects Aged ≥ 70 Years Who Received 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Evaluable Immunogenicity Population)

	Vaccine Sequence (As Randomized)						GMT Ratio (23vPS / PCV13 to PCV13) and 95% CI	
	23vPS/PCV13[a]			PCV13				
Serotype	**n[b]**	**GMT[c]**	**95% CI[d]**	**n[b]**	**GMT[c]**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	367	34	29, 41	426	81	68, 96	0.4	**0.33** , **0.54**
3	362	33	28, 38	405	55	48, 63	0.6	**0.49** , **0.74**
4	338	267	210, 340	400	545	442, 672	0.5	**0.36** , **0.67**
5	362	42	34, 51	422	72	60, 87	0.6	**0.44** , **0.76**
6B	352	721	566, 919	411	1261	1025, 1553	0.6	**0.42** , **0.78**
7F	357	120	91, 159	420	245	192, 312	0.5	**0.34** , **0.71**
9V	349	72	53, 96	402	181	138, 237	0.4	**0.27** , **0.59**
14	361	194	154, 245	411	280	228, 346	0.7	0.51 , **0.95**
18C	360	513	413, 637	411	907	762, 1080	0.6	**0.43** , **0.74**
19A	362	248	211, 291	420	354	308, 408	0.7	0.56 , **0.86**
19F	358	180	145, 224	414	333	273, 405	0.5	**0.40** , **0.72**
23F	349	87	67, 113	403	158	126, 199	0.6	**0.39** , **0.78**
6A	352	549	437, 690	421	903	727, 1121	0.6	**0.44** , **0.83**

[a] PCV13 administered one year after an initial study dose of 23vPS.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] GMTs were calculated using all subjects with available data for both the specified blood draws.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs is calculated by back transforming the mean difference between vaccine group/sequence on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (23vPS / PCV13– PCV13).
This table represents descriptive results from an exploratory study objective.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, page73 (Table 9-9).

Complete Results: GMTs after each Vaccination and Sequence (Table 23)

Table 23: Study 6115A1-3005. Pneumococcal OPA GMTs for All Vaccine Groups/Sequences[a] in Subjects Aged ≥ 70 Years Who Received 1 Dose of 23vPS at Least 5 Years Prior to Enrollment (Evaluable Immunogenicity Population)

			Sampling Time					
			Pre-Vaccination[b]			Post-Vaccination[b]		
Serotype	Dose #	Vaccine / Sequence (as randomized)	n[c]	GMT[d]	95% CI[e]	n[c]	GMT[d]	95% CI[e]
1	1	PCV13	428	10	9, 12	426	81	68, 96
		23vPS	442	10	9, 12	445	55	46, 65
	2	PCV13 / PCV13	371	30	25, 36	370	76	65, 90
		23vPS / PCV13	371	21	18, 26	367	34	29, 41
3	1	PCV13	410	9	8, 11	405	55	48, 63
		23vPS	426	10	9, 12	424	49	43, 57
	2	PCV13 / PCV13	355	18	16, 21	362	55	48, 62
		23vPS / PCV13	357	16	14, 19	362	33	28, 38
4	1	PCV13	381	29	23, 38	400	545	442, 672
		23vPS	391	27	21, 34	395	203	157, 262
	2	PCV13 / PCV13	339	148	113, 195	347	472	384, 580
		23vPS / PCV13	331	72	54, 95	338	267	210, 340
5	1	PCV13	422	11	10, 13	422	72	60, 87
		23vPS	440	11	10, 13	442	36	30, 43
	2	PCV13 / PCV13	370	27	23, 33	365	56	47, 68
		23vPS / PCV13	370	20	17, 25	362	42	34, 51
6A	1	PCV13	416	22	18, 27	421	903	727, 1121
		23vPS	423	28	22, 35	433	94	74, 119
	2	PCV13 / PCV13	363	286	224, 366	366	1134	944, 1364
		23vPS / PCV13	355	53	41, 69	352	549	437, 690
6B	1	PCV13	386	77	59, 100	411	1261	1025, 1553
		23vPS	395	96	74, 125	411	417	331, 527
	2	PCV13 / PCV13	353	381	297, 489	356	1565	1306, 1876
		23vPS / PCV13	349	170	130, 223	352	721	566, 919
7F	1	PCV13	420	22	18, 28	420	245	192, 312
		23vPS	428	19	15, 24	431	160	124, 208
	2	PCV13 / PCV13	361	53	40, 69	365	185	143, 240
		23vPS / PCV13	358	53	42, 71	357	120	91, 159
9V	1	PCV13	393	19	15, 25	402	181	138, 237
		23vPS	403	23	18, 30	402	90	68, 120
	2	PCV13 / PCV13	351	35	27, 47	356	158	120, 210
		23vPS / PCV13	346	24	18, 32	349	72	53, 96
14	1	PCV13	410	87	68, 111	411	280	228, 346
		23vPS	415	85	66, 108	410	285	229, 354
	2	PCV13 / PCV13	366	139	110, 176	366	238	192, 294
		23vPS / PCV13	359	123	96, 157	361	194	154, 245

			Sampling Time					
			Pre-Vaccination[b]			Post-Vaccination[b]		
Serotype	**Dose #**	**Vaccine / Sequence (as randomized)**	**n[c]**	**GMT[d]**	**95% CI[e]**	**n[c]**	**GMT[d]**	**95% CI[e]**
18C	1	PCV13	408	122	97, 154	411	907	762, 1080
		23vPS	420	119	94, 150	416	481	385, 601
	2	PCV13 / PCV13	362	381	311, 466	361	975	829, 1147
		23vPS / PCV13	365	244	192, 311	360	513	413, 637
19A	1	PCV13	422	79	67, 94	420	354	308, 408
		23vPS	437	71	59, 85	442	200	170, 234
	2	PCV13 / PCV13	365	170	146, 199	362	339	296, 387
		23vPS / PCV13	368	125	104, 150	362	248	211, 291
19F	1	PCV13	412	45	36, 56	414	333	273, 405
		23vPS	420	38	30, 47	417	214	174, 263
	2	PCV13 / PCV13	356	110	89, 137	354	311	257, 376
		23vPS / PCV13	354	86	68, 110	358	180	145, 224
23F	1	PCV13	410	14	12, 17	403	158	126, 199
		23vPS	415	15	12, 18	417	43	34, 54
	2	PCV13 / PCV13	357	54	43, 68	360	310	254, 378
		23vPS / PCV13	353	26	21, 32	349	87	67, 113

[a] Vaccinations administered as a two dose sequence were administered 1 year apart.
[b] For vaccination 1, prevaccination is the blood draw before vaccination 1 and postvaccination is the blood draw 1 month after vaccination 1. For vaccination 2, prevaccination is the blood draw before vaccination 2 and postvaccination is the blood draw 1 month after vaccination 2.
[c] Number of subjects with valid and determinate OPA antibody titer for the specified serotype at the given visit.
[d] GMTs calculated using all subjects with available data for the specified blood draw.
[e] CIs are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
This table represents descriptive results from this study.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, pages 78-79 (Table 9-13).

6.0 Supportive Clinical Immunogenicity Studies

6.1 Study 6115A1-3010 (NCT00574548)

Title: A phase 3, randomized, active-controlled, modified double-blind trial to evaluate safety, tolerability, and immunogenicity of Prevnar 13 when administered over 12 months either as a 2-dose regimen or with 23vPS vaccine in healthy adults 60 to 64 years of age who are naïve to 23vPS.

6.1.1 Study Design

Study 6115A1-3010 is a phase 3, parallel group, randomized (3:5:4), active controlled, modified double-blind, multicenter trial.

Table 24: Study 3010 Design.

Subjects	Group #	N (planned enrollment)	N (planned evaluable)	Vaccination	
				Year 0	Year 1
Healthy 60-64 year old adults naïve to 23vPS	1.1	180	150	PCV13	PCV13
	1.2	300	250	PCV13	23vPS
	2.0	240	200	23vPS	PCV13
	Total	720	600		

Source: 125324/262.0,m5.3.5.1.3, CSR-76150-report body, page 20 (Table 6-1).

6.1.2 Study Objectives

The main goal of this study was to demonstrate if it is preferable to administer a dose of pneumococcal conjugate vaccine prior to a dose of polysaccharide vaccine. A 1-year interval between doses was chosen in order to better detect any potential reduction in response when 2 doses of conjugate vaccine were administered. The study was designed to meet the following objectives:

Primary Objectives

1. To demonstrate that the immune response to 23vPS administered 1 year after an initial study dose of PCV13 (Group 1.2) is noninferior to the immune response to an initial study dose of 23vPS (Group 2.0) for the 12 common serotypes as measured by serotype-specific OPA GMTs obtained 1 month after vaccination. That is, the lower bound of the 95% CI of the GMT ratio ($GMT_{PCV13/\underline{23vPS}}$ / $GMT_{\underline{23vPS}}$) is greater than 0.5 (2-fold criterion).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

2. To demonstrate that the immune response to 23vPS administered 1 year after an initial study dose of PCV13 (Group 1.2) is noninferior to the immune response to PCV13 administered 1 year after an initial study dose of 23vPS (Group 2.0) for the 12 common serotypes in PCV13, as measured by serotype-specific OPA GMTs 1 month

after vaccination. That is, the lower bound of the 95% CI of the GMT ratio ($GMT_{PCV13/23vPS}$ / $GMT_{23vPS/13PnC}$) is greater than 0.5 (2-fold criterion).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

Secondary Objectives

1. To demonstrate that the immune response to a second dose of PCV13 administered 1 year after an initial study dose of PCV13 (Group 1.1) is noninferior to the immune response to the initial dose of PCV13, as measured by serotype-specific OPA GMTs 1 month after year 0 and year 1 vaccinations. That is, the lower bound of the 95% CI of the GMT ratio ($GMT_{PCV13/PCV13}$ / GMT_{PCV13}) is greater than 0.5.

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

2. To demonstrate that the immune response to 23vPS administered 1 year after an initial study dose of PCV13 (Group 1.2) is noninferior to the immune response to an initial study dose of PCV13 as measured by serotype-specific OPA titers 1 month after vaccination. That is, the lower bound of the 95% CI of the GMFR ($GMT_{PCV13/23vPS}$ / GMT_{PCV13}) is greater than 0.5.

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

3. To demonstrate that 23vPS administered 1 year after an initial study dose of PCV13 is statistically significantly more immunogenic than an initial study dose of 23vPS for at least some of the 12 common serotypes[1] as measured by serotype-specific OPA GMTs obtained 1 month after vaccination ($GMT_{PCV13/23vPS}$ / GMT_{23vPS}).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

1 Statistical statistically significantly greater responses cannot be shown for serotype 6B; however with the specified sample sizes non-inferiority within 1.5 fold is achievable.

4. To demonstrate that 23vPS administered 1 year after an initial study dose of PCV13 is statistically significantly more immunogenic than PCV13 administered 1 year after an initial study dose of 23vPS for at least some of the 12 common serotypes[1] as measured by serotype-specific OPA GMTs obtained 1 month after vaccination (GMT_{PCV13} / $GMT_{23vPS/PCV13}$).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

5. To demonstrate that an initial dose of PCV13 is statistically significantly more immunogenic than PCV13 administered 1 year after an initial dose of 23vPS for at least some of the 12 common serotypes as measured by serotype-specific OPA GMTs 1 month after vaccination (GMT_{PCV13}/$GMT_{23vPS/PCV13}$).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

Exploratory Objectives

To evaluate the immune response to 23vPS administered 1 year after an initial study dose of PCV13 relative to the immune response to the initial study dose of 23vPS as measured by anti-6A OPA titers obtained 1 month after vaccination (PCV13 / 23vPS vs 23vPS). Criteria for statistically significantly greater response: Lower limit of the exact, unconditional, 2-sided, 95% CI for the difference in proportions of subjects (PCV13-23vPS) achieving a 4-fold rise is > 0.

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

To evaluate the immune response to 23vPS administered 1 year after an initial study dose of PCV13 relative to the immune response to PCV13 administered 1 year after an initial study dose of 23vPS as measured by anti-6A OPA titers obtained 1 month after vaccination (23vPS/PCV13 vs PCV13). Criteria for statistically significantly greater response (1 month after year 0 dose): Lower limit of the exact, unconditional, 2-sided, 95% CI for the difference in proportions of subjects (PCV13-23vPS) achieving a 4-fold rise is > 0.

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

1. To evaluate the immune response to PCV13 administered 1 year after an initial study dose of 23vPS relative to the immune response to the initial study dose of PCV13 as measured by anti-6A OPA titers obtained 1 month after vaccination (23vPS/PCV13 vs PCV13).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

2. To evaluate the immune response to 23vPS administered 1 year after an initial study dose of PCV13 relative to the immune response to the initial study dose of PCV13 as measured by anti-6A OPA titers obtained 1 month after vaccination (PCV13/23vPS vs PCV13).

Group	Vaccination	
	Year 0	Year 1
1.1	PCV13	PCV13
1.2	PCV13	23vPS
2.0	23vPS	PCV13

6.1.3 Populations Analyzed

Two analysis populations were defined for immunogenicity analyses at each of the two study doses. The all-available population included all subjects who had at least 1 valid and determinate assay result related to that vaccination. The evaluable immunogenicity population for vaccination 1 was identical to the evaluable immunogenicity population for cohort 1 of study 004. The evaluable immunogenicity population for vaccination 2 was similar to vaccination 1; however the allowable time frames related to vaccination 2 and the allowable time window for receipt of vaccination 2 was within 351 to 379 days after vaccination 1.

6.1.4 Immunogenicity Results

Primary Immunogenicity Objectives

12 Common Serotypes: Non-inferiority Based on OPA GMTs One Month After PCV13/23vPS (given 1 year apart) Compared to Initial Dose of 23vPS (Table 25)
For the 12 common serotypes, the criterion for demonstrating non-inferiority of immune responses at year 1 following a sequence of PCV13/23vPS compared to the immune responses after an initial dose of 23vPS was a lower limit of the 2-sided 95% CI for the GMT ratio > 0.5. This criterion was met for each of the 12 common serotypes. The lower limit of the 95% CI was > 1.0 for 6 of the 12 common serotypes (serotypes 3, 5, 6B, 7F, 19F, and 23F).

Table 25. Study 6115A1-3010. Pneumococcal OPA GMTs for the 12 Common Serotypes 1 Month After PCV13/23vPS[s] and an initial dose of 23vPS in 23vPS-Naïve Adults Aged 60 to 64 Years (Evaluable Immunogenicity Population)

	Vaccine Group/Sequence As Randomized						GMT Ratio [(PCV13/23vPS) / 23vPS] and 95% CI	
	PCV13/23vPS[a]			23vPS				
Serotype	n[b]	GMT	95% CI[c]	n[b]	GMT	95% CI[c]	Ratio[d]	95% CI[e]
1	231	148	124, 177	227	148	118, 186	1.0	0.75, 1.33
3	228	125	109, 143	229	80	68, 96	1.6	1.24, 1.94
4	232	1385	1171, 1639	220	1357	1023, 1799	1.0	0.74, 1.41
5	218	199	161, 246	224	140	107, 184	1.4	1.01, 2.00
6B	231	1215	965, 1528	219	706	522, 954	1.7	1.18, 2.51
7F	227	537	422, 683	219	331	234, 469	1.6	1.07, 2.47
9V	229	373	268, 518	215	288	198, 419	1.3	0.79, 2.12
14	231	622	486, 796	218	734	544, 990	0.8	0.58, 1.25
18C	226	1062	863, 1308	224	789	586, 1062	1.3	0.94, 1.93
19A	216	467	404, 541	218	376	303, 466	1.2	0.96, 1.61
19F	222	774	642, 934	217	509	386, 673	1.5	1.09, 2.12
23F	233	198	151, 259	214	70	50, 97	2.8	1.86, 4.35

[a] 23vPS administered one year after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[e] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures ([PCV13/23vPS] – 23vPS).
Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
This table presents results from a co-primary and co-secondary study objective.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-report body, pages 60-61 (Table 9-3).

12 Common Serotypes: Non-inferiority Based on OPA GMTs One Month After PCV13/23vPS (given 1 year apart) Compared to 23vPS/PCV13 (given 1 year apart) (Table 26)

For the 12 common serotypes, the criterion for demonstrating non-inferiority of the immune response following a sequence of PCV13/23vPS compared to the immune response following a sequence of 23vPS/PCV13 was a lower limit of the 2-sided 95% CI for the GMT ratio > 0.5. This criterion was met for each of the 12 common serotypes. The lower limit of the 95% CI was > 1.0 for 11 of the 12 common serotypes.

Table 26. Study 6115A1-3010. Pneumococcal OPA GMTs for the 12 Common Serotypes 1 Month After PCV13/23vPS[a] Compared to 23vPS/PCV13[b] in 23vPS-Naïve Adults Aged 60 to 64 years (Evaluable Immunogenicity Population)

	Vaccine Sequence As Randomized						GMT Ratio [(PCV13/23vPS) / (23vPS/PCV13)] and 95% CI	
	PCV13/23vPS[a]			23vPS/PCV13[b]				
Serotype	**n[c]**	**GMT**	**95% CI[d]**	**n[c]**	**GMT**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	231	148	124, 177	196	77	61, 98	1.9	1.43, 2.57
3	228	125	109, 143	190	50	41, 62	2.5	1.95, 3.16
4	232	1385	1171, 1639	192	935	740, 1182	1.5	1.12, 1.96
5	218	199	161, 246	180	85	64, 112	2.4	1.67, 3.31
6B	231	1215	965, 1528	191	710	529, 953	1.7	1.19, 2.47
7F	227	537	422, 683	189	126	86, 185	4.3	2.76, 6.61
9V	229	373	268, 518	187	114	77, 169	3.3	1.97, 5.45
14	231	622	486, 796	193	435	323, 586	1.4	0.98, 2.10
18C	226	1062	863, 1308	192	564	418, 762	1.9	1.32, 2.69
19A	216	467	404, 541	184	289	236, 354	1.6	1.27, 2.07
19F	222	774	642, 934	187	286	217, 377	2.7	1.96, 3.74
23F	233	198	151.2, 259.4	192	124	88.2, 173.0	1.6	1.05, 2.45

[a] 23vPS administered one year after an initial study dose of PCV13.
[b] PCV13 administered one year after an initial study dose of 23vPS.
[c] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures ([PCV13/23vPS] – [23vPS/PCV13]).
Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
This table presents results from a co-primary and co-secondary study objective.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-report body, page 62 (Table 9-4).

Secondary Immunogenicity Objectives

12 Common Serotypes: Statistically Significantly Greater Responses Based on OPA GMTs One Month Post-vaccination (Tables 25 – 27)

For the 12 common serotypes, the criterion for demonstrating statistically significantly greater OPA GMTs after PCV13/23vPS (given 1 year apart) compared to the immune responses after an initial dose of 23vPS was a lower limit of the 2-sided 95% CI for the GMT ratio > 1.0. This criterion was met by 6 of the 12 common serotypes (serotypes 3, 5, 6B, 7F, 19F, and 23F) (Table 25).

For the 12 common serotypes, the criterion for demonstrating statistically significantly greater immune responses after PCV13/23vPS (given 1 year apart) compared to the immune responses after 23vPS/PCV13 (given 1 year apart) was a lower limit of the 2-sided 95% CI for the GMT ratio > 1.0. This criterion was met for 11 of the 12 common serotypes (all except serotype 14) (Table 26). In the all-available population, the lower limit of the 95% CI was > 1.0 for all 12 common serotypes (data not shown).

The criterion for demonstrating statistically significantly greater immune responses after an initial dose of PCV13 compared to the immune response after 23vPS/PCV13 (given 1 year apart) was a lower limit of the 2-sided 95% CI for the GMT ratio > 1.0. This criterion was met by all 12 common serotypes (Table 27).

Table 27. Study 6115A1-3010. Pneumococcal OPA GMTs for the 12 Common Serotypes 1 Month After PCV13 and 23vPS/PCV13[a] in 23vPS-Naïve Adults Aged 60 to 64 years (Evaluable Immunogenicity Population)

	Vaccine Group/Sequence As Randomized						GMT Ratio [PCV13 / (23vPS/PCV13)] and 95% CI	
	PCV13			23vPS/PCV13[a]				
Serotype	n[b]	GMT	95% CI[c]	n[b]	GMT	95% CI[c]	Ratio[d]	95% CI[e]
1	451	207	178, 241	196	77	61, 98	2.7	2.03, 3.55
3	455	75	66, 85	190	50	41, 62	1.5	1.18, 1.89
4	454	2536	2192, 2933	192	935	740, 1182	2.7	2.07, 3.55
5	432	215	176, 262	180	85	64, 112	2.5	1.77, 3.61
6B	447	1948	1614, 2352	191	710	529, 953	2.7	1.94, 3.88
7F	450	1063	869, 1302	189	126	86, 185	8.5	5.68, 12.60
9V	442	767	620, 949	187	114	77, 169	6.7	4.45, 10.22
14	441	650	525, 806	193	435	323, 586	1.5	1.02, 2.18
18C	436	1576	1321, 1881	192	564	418, 762	2.8	2.01, 3.89
19A	410	709	619, 811	184	289	236, 354	2.5	1.92, 3.13
19F	433	711	596, 849	187	286	217, 377	2.5	1.80, 3.44
23F	449	354	284, 441	192	124	88, 173	2.9	1.92, 4.28

[a] PCV13 administered one year after an initial study dose of 23vPS.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[e] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13 – [23vPS/PCV13]).

Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMT ratio was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
This table presents results from a co-secondary study objective.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-report body, page 63 (Table 9-5).

13 Vaccine Serotypes: OPA GMT GMFR (Table 28)

Non-inferiority was achieved after PCV13/PCV13 (given 1 year apart) compared to an initial dose of PCV13 for 9 of the 13 vaccine serotypes (i.e., the lower limit of the 95% CI for the GMFR was > 0.5). Statistically significantly greater OPA GMTs were achieved for 1 of the serotypes (23F) (i.e., the lower limit of the 2-sided 95% CI for the GMFR was > 1.0). Statistically significantly lower OPA GMTs were achieved after PCV13/PCV13 compared to PCV13 for 7 of the 13 serotypes (i.e. the upper limit of the 95% CI of the GMFR was < 1.0).

Table 28. Study 6115A1-3010. Pneumococcal OPA GMTs After PCV13/PCV13[a] and PCV13 in 23vPS-Naïve Adults Aged 60 to 64 years (Evaluable Immunogenicity Population)

	Vaccine Sequence As Randomized						GMFR [(PCV13/PCV13) / PCV13] and 95% CI	
	PCV13/PCV13[a]			PCV13				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**GMFR[d]**	**95% CI[c]**
1	123	142	112, 180	123	215	164, 282	0.7	0.54, **0.82**
3	117	89	75, 105	117	73	57, 94	1.2	0.99, 1.49
4	126	1214	932, 1582	126	2255	1625, 3129	0.5	**0.43**, **0.68**
5	115	98	70, 137	115	170	112, 259	0.6	**0.43**, **0.77**
6A	126	2281	1747, 2979	126	2682	1970, 3652	0.9	0.67, 1.08
6B	118	1882	1430, 2478	118	2112	1508, 2958	0.9	0.71, 1.12
7F	125	323	216, 483	125	930	602, 1437	0.3	**0.24**, **0.49**
9V	116	335	215, 523	116	919	619, 1364	0.4	**0.26**, **0.51**
14	120	384	262, 561	120	492	313, 775	0.8	0.60, 1.02
18C	120	986	731, 1330	120	1440	1015, 2044	0.7	0.54, **0.87**
19A	102	385	308, 482	102	583	427, 797	0.7	0.53, **0.82**
19F	115	502	381, 662	115	566	386, 829	0.9	0.69, 1.15
23F	127	456	322, 645	127	291	188, 452	1.6	1.15, 2.13

[a] PCV13 administered one year after an initial study dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype at both blood draws.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or mean fold rises.
[d] GMFRs calculated using all evaluable subjects with data from both the post-vaccination 1 and post-vaccination 2 blood draws.
This table presents results from a co-secondary study objective. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMFR was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-report body, page 64 (Table 9-6).

12 Common Serotypes: OPA GMT GMFR (Table 29)
The criterion for demonstrating that immune responses after the PCV13/23vPS (given 1 year apart) are non-inferior to immune responses to an initial dose of PCV13 (Yr 0) was a lower limit of the 95% CI for the GMFR > 0.5. This criterion was met by 8 of the 12 common serotypes. The criterion for demonstrating statistically significantly greater immune responses was a lower limit of the 2-sided 95% CI for the GMFR > 1.0. This criterion was met for 1 serotype (type 3). Statistically significantly lower immune responses were elicited after PCV13/PCV13 compared to PCV13 (i.e. an upper limit of the 95% CI of the GMFR < 1.0) for 8 of the 12 common serotypes.

Table 29. Study 6115A1-3010. Pneumococcal OPA GMTs and GMFRs for the 12 Common Serotypes After PCV13 and PCV13/23vPS[a] in 23vPS-Naïve Adults Aged 60 to 64 years (Evaluable Immunogenicity Population)

	Vaccine Sequence As Randomized						GMFR [(PCV13/23vPS) / PCV13] and 95% CI	
	PCV13/23vPS[a]			PCV13				
Serotype	**n[b]**	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**	**GMFR[d]**	**95% CI[c]**
1	220	140	117, 168	220	220	179, 269	0.6	0.55, **0.75**
3	219	129	112, 148	219	74	61, 89	1.7	1.52, 2.01
4	220	1430	1215, 1684	220	2517	2092, 3029	0.6	**0.49**, **0.66**
5	199	188	151, 235	199	227	171, 301	0.8	0.67, 1.03
6B	220	1351	1088, 1677	220	2012	1572, 2574	0.7	0.57, **0.79**
7F	215	533	419, 678	215	1252	971, 1614	0.4	**0.35**, **0.52**
9V	217	406	292, 565	217	758	564, 1019	0.5	**0.41**, **0.69**
14	214	616	473, 802	214	664	485, 909	0.9	0.75, 1.15
18C	207	1074	872, 1322	207	1532	1184, 1983	0.7	0.58, **0.85**
19A	189	457	390, 536	189	696	581, 834	0.7	0.58, **0.74**
19F	204	773	637, 938	204	696	546, 888	1.1	0.89, 1.39
23F	221	216	165, 283	221	358	266, 482	0.6	**0.50**, **0.73**

[a] 23vPS administered one year after an initial dose of PCV13.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype at both blood draws.
[b] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or mean fold rises.
[c] GMFRs were calculated using all evaluable subjects with data from both the post-vaccination 1 and post-vaccination 2 blood draws.
This table presents results from a co-secondary study objective. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMFR was > 0.5. Success criteria were met for demonstrating statistically significantly greater and statistically significantly lower responses when the lower-limit of the 95% CI was > 1 and when the upper limit of the 95% CI was < 1, respectively.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-report body, page 64 (Table 9-7).

Exploratory Immunogenicity Objective

Serotype 6A (Table 30)
As an exploratory objective, OPA antibody titers to serotype 6A and the 12 common serotypes are summarized by GMTs and corresponding 95% CIs in Table 30. No formal comparisons were pre-specified in the final protocol.

Complete Results: GMTs after each Vaccination and Sequence

Table 30: Study 6115A1-3010. Pneumococcal OPA GMTs for all Vaccine Groups/Sequences[a] (Evaluable Immunogenicity Population)

			Sampling Time					
			Pre-Vaccination[a]			1 Month Post-Vaccination[a]		
Serotype	Dose #	Vaccine / Sequence (as randomized)	n[b]	GMT[c]	95% CI[d]	n[b]	GMT[c]	95% CI[d]
1	1	PCV13	449	6	6, 7	449	206	177, 240
		23vPS	226	7	6, 8	226	149	118, 187
	2	PCV13 / PCV13	128	54	40, 73	128	140	110, 177
		PCV13 / 23vPS	225	57	45, 70	225	148	124, 178
		23vPS / PCV13	192	47	37, 61	192	76	60, 97
3	1	PCV13	444	6	5, 6	444	75	65, 85
		23vPS	224	6	6, 7	224	79	66, 94
	2	PCV13 / PCV13	117	20	15, 26	117	91	77, 107
		PCV13 / 23vPS	214	24	19, 29	214	122	106, 142
		23vPS / PCV13	182	26	21, 32	182	51	41, 63
4	1	PCV13	396	39	29, 51	396	2418	2059, 2840
		23vPS	198	32	22, 48	198	1327	978, 1799
	2	PCV13 / PCV13	119	646	445, 938	119	1262	957, 1666
		PCV13 / 23vPS	224	597	454, 784	224	1426	1209, 1682
		23vPS / PCV13	177	394	285, 545	177	942	737, 1203
5	1	PCV13	428	6	5, 6	428	213	175, 261
		23vPS	217	5	5, 6	217	134	102, 177
	2	PCV13 / PCV13	115	39	26, 57	115	96	68, 136
		PCV13 / 23vPS	206	61	46, 81	206	202	162, 251
		23vPS / PCV13	175	49	36, 65	175	85	64, 112
6A	1	PCV13	423	19	156, 24	423	2734	2285, 3273
		23vPS	208	14	10, 19	208	250	172, 362
	2	PCV13 / PCV13	125	493	318, 765	125	2410	1839, 3158
		PCV13 / 23vPS	217	692	523, 915	217	1348	1079, 1685
		23vPS / PCV13	175	92	62, 136	175	1145	874, 1501
6B	1	PCV13	394	33	25, 43	394	1903	1551, 2336
		23vPS	199	26	18, 38	199	632	456, 877
	2	PCV13 / PCV13	117	486	314, 753	117	1894	1436, 2498
		PCV13 / 23vPS	224	466	341, 635	224	1210	955, 1532
		23vPS / PCV13	180	182	125, 265	180	709	522, 963
7F	1	PCV13	429	7	6, 9	429	1009	818, 1245
		23vPS	207	7	6, 9	207	305	213, 437
	2	PCV13 / PCV13	124	149	93, 241	124	323	213, 490
		PCV13 / 23vPS	217	111	78, 158	217	523	410, 667
		23vPS / PCV13	179	65	43, 96	179	120	81, 179
9V	1	PCV13	399	14	11, 18	399	747	597, 937

			Sampling Time					
			Pre-Vaccination[a]			1 Month Post-Vaccination[a]		
Serotype	**Dose #**	**Vaccine / Sequence (as randomized)**	**n[b]**	**GMT[c]**	**95% CI[d]**	**n[b]**	**GMT[c]**	**95% CI[d]**
		23vPS	194	16	12, 23	194	285	191, 424
	2	PCV13 / PCV13	120	106	64, 175	120	340	219, 528
		PCV13 / 23vPS	223	73	51, 106	223	360	257, 504
		23vPS / PCV13	174	53	35, 81	174	116	77, 176
14	1	PCV13	410	31	24, 40	410	623	498, 780
		23vPS	202	46	32, 66	202	716	523, 982
	2	PCV13 / PCV13	123	206	134, 316	123	391	269, 567
		PCV13 / 23vPS	225	257	188, 351	225	614	477, 791
		23vPS / PCV13	187	298	214, 416	187	418	308, 568
18C	1	PCV13	414	25	20, 30	414	1604	1338, 1923
		23vPS	215	32	23, 45	215	755	556, 1027
	2	PCV13 / PCV13	122	416	282, 615	122	996	738, 1344
		PCV13 / 23vPS	221	442	337, 582	221	1052	851, 1301
		23vPS / PCV13	182	325	230, 459	182	541	398, 736
19A	1	PCV13	381	24	20, 29	381	699	606, 806
		23vPS	200	25	19, 32	200	366	291, 461
	2	PCV13 / PCV13	115	194	143, 263	115	413	337, 507
		PCV13 / 23vPS	203	198	162, 242	203	461	397, 536
		23vPS / PCV13	179	142	109, 187	179	291	236, 358
19F	1	PCV13	404	20	16, 24	404	726	607, 869
		23vPS	205	16	12, 22	205	491	368, 657
	2	PCV13 / PCV13	115	135	88, 206	115	478	363, 629
		PCV13 / 23vPS	209	161	120, 216	209	778	641, 945
		23vPS / PCV13	171	134	96, 187	171	277	208, 370
23F	1	PCV13	427	9	8, 11	427	332	265, 417
		23vPS	200	8	6, 10	200	64	45, 90
	2	PCV13 / PCV13	120	76	49, 118	120	434	302, 623
		PCV13 / 23vPS	227	86	64, 117	227	202	154, 266
		23vPS / PCV13	183	31	22, 43	183	122	87, 173

[a] Vaccinations administered as a two dose sequence were administered 1 year apart.
[b] Statistical analysis plan–specified timing for blood sample collection.
[c] For vaccination 1, prevaccination is the blood draw before vaccination 1 and postvaccination is the blood draw 1 month after vaccination 1. For vaccination 2, prevaccination is the blood draw before vaccination 2 and postvaccination is the blood draw 1 month after vaccination 2.
[d] n = Number of subjects with a determinate OPA antibody titer to the given serotype at both blood draws.
[e] GMTs were calculated using all evaluable subjects with data for both the specified blood draws.
[f] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers, or mean fold rises.
Source: 125324/262.0,m5.3.5.1.3, CSR-76436-report body, pages 67-70 (Table 9-8).

Additional Vaccine Sequence Comparisons
Additional comparisons were made between vaccine sequences after completion of the original clinical study reports applying the same statistical rules as used in the planned analyses.

23vPS/PCV13 (given 1 year apart) relative to an initial dose of 23vPS (Table 31)
Statistically significantly lower OPA GMTs were observed (i.e., the upper limit of the 95% CI for the GMFRs was < 1.0) after 23vPS/PCV13 relative to 23vPS for 10 of 12 common serotypes (all except serotypes 6B and 23F). Statistically significantly greater OPA GMTs were observed for serotypes 6A and 6B after 23vPS/PCV13 than after 23vPS for serotype 23F (i.e., the lower limit of the 95% CI for the GMFR was > 1.0). OPA GMTs were similar between the two groups for serotype 6B. However, among subjects who received PCV13 one year after an initial dose of 23vPS (i.e. 23vPS/PCV13), GMTs were higher one-month after receipt of PCV13 compared to pre-vaccination titers just prior to the administration of PCV13.

Table 31. Study 6115A1-3010. Pneumococcal OPA GMTs After 23vPS and 23vPS/PCV13[a] in 23vPS-Naïve Adults Aged 60 to 64 Years (Evaluable Immunogenicity Population)

	Vaccine Sequence As Randomized						GMFR [(23vPS/PCV13) / 23vPS] and 95% CI	
	23vPS/PCV13[a]			23vPS				
Serotype	**n[b]**	**GMT[c]**	**95% CI[d]**	**n[b]**	**GMT[c]**	**95% CI[d]**	**GMFR[e]**	**95% CI[d]**
1	189	73	57, 93	189	153	119, 197	0.5	**0.40**, **0.57**
3	185	51	42, 63	185	84	70, 102	0.6	0.51, **0.72**
4	177	907	705, 1166	177	1391	1032, 1873	0.7	0.52, **0.81**
5	171	86	65, 115	171	144	107, 195	0.6	**0.49**, **0.73**
6A	182	1120	864, 1452	182	347	239, 505	3.2	2.23, 4.68
6B	178	719	537, 963	178	772	559, 1066	0.9	0.71, 1.22
7F	179	113	76, 167	179	345	234, 508	0.3	**0.22**, **0.48**
9V	171	113	75, 171	171	314	208, 475	0.4	**0.24**, **0.54**
14	179	443	327, 600	179	737	527, 1031	0.6	**0.48**, **0.75**
18C	180	546	401, 742	180	870	632, 1199	0.6	0.51, **0.77**
19A	171	278	225, 345	171	382	300, 487	0.7	0.62, **0.86**
19F	172	283	212, 378	172	504	371, 685	0.6	**0.44**, **0.71**
23F	178	120	85, 171	178	78	54, 112	1.5	1.17, 2.05

[a] PCV13 administered one year after an initial study dose of 23vPS.
[b] n = number of subjects with a determinate OPA antibody titer to the specified serotype at both blood draws.
[c] GMTs calculated using all subjects with available data from both after vaccination 1 (Yr 0) and after vaccination 2 (Yr 1) blood draws.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers or mean fold rises.
[e] GMFRs calculated using all evaluable subjects with data from both the post-vaccination 1 and post-vaccination 2 blood draws.
This table represents descriptive results from this study.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-addendum, page 14 (Table 5.4).

PCV13/PCV13 (given 1 year apart) relative to PCV13/23vPS (given 1 year apart) (Table 32)

The upper limit of the 2-sided 95% CI for the GMT ratio [PCV13/PCV13 to PCV13/23vPS] was observed to be less than 1 for 5 of the 12 common serotypes. This suggests that OPA GMTs were statistically significantly lower for 5 of the 12 common serotypes (3, 5, 7F, 14, and 19F) following PCV13/PCV13 compared to PCV13/23vPS. Non-inferiority (i.e., a lower limit of the 95% CI for the GT ratio > 0.5) was observed for 8 of 12 common serotypes (all except 5, 7F, 14, and 19F). The lower limit of the 2-sided 95% CI for the GMT ratio was observed to be greater than 1 for 2 serotypes (6B and 23F). This suggests that the OPA GMTs were statistically significantly greater following PCV13/PCV13 compared to PCV13/23vPS.

Table 32. Study 6115A1-3010. Pneumococcal OPA GMTs After PCV13/PCV13[a] and PCV13/23vPS[b] in 23vPS-Naïve Adults Aged 60 to 64 Years (Evaluable Immunogenicity Population)

	Vaccine Group/Sequence As Randomized						GMT Ratio [(PCV13/PCV13) / (PCV13/23vPS)] and 95% CI	
	PCV13/PCV13[a]			PCV13/23vPS[b]				
Serotype	**n[c]**	**GMT[d]**	**95% CI[e]**	**n[c]**	**GMT[d]**	**95% CI[e]**	**Ratio[f]**	**95% CI[g]**
1	129	139	110, 176	231	148	124, 177	0.9	0.70, 1.26
3	121	89	76, 105	228	125	109, 143	0.7	0.57, **0.89**
4	128	1212	934, 1573	232	1385	1171, 1639	0.9	0.65, 1.18
5	121	96	69, 135	218	199	161, 246	0.5	**0.33**, **0.70**
6A	131	2354	1814, 3056	225	1268	1010, 1592	1.9	1.30, 2.66
6B	124	1879	1446, 2444	231	1215	965, 1528	1.5	1.07, 2.23
7F	130	335	225, 500	227	537	422, 683	0.6	**0.40**, **0.97**
9V	124	356	232, 547	229	373	268, 518	1.0	0.55, 1.65
14	127	389	271, 559	231	622	486, 796	0.6	**0.41**, **0.96**
18C	127	1015	760, 1354	226	1062	863, 1308	1.0	0.67, 1.36
19A	121	410	334, 503	216	467	404, 541	0.9	0.69, 1.12
19F	125	501	385, 652	222	774	642, 934	0.6	**0.47**, **0.89**
23F	131	472	337, 663	233	198	151, 259	2.4	1.54, 3.70

[a] PCV13 administered one year after an initial study dose of PCV13.
[b] 23vPS administered one year after an initial study dose of PCV13.
[c] n = number of subjects with a determinate OPA antibody titer to the specified serotype.
[d] GMTs calculated using all subjects with available data for the specified blood draw.
[e] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[f] Ratio of GMTs [PCV13/PCV13 to PCV13/23vPS] calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[g] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13/PCV13 – PCV13/23vPS).
This table presents descriptive data.
Source: 125324/262.0,m5.3.5.1.3, CSR-76150-addendum, page 15 (Table 5.5).

7.0 Concomitant Vaccine Evaluation

Two studies, 6115A1-3001 and -3008, comprised the supportive studies to demonstrate that TIV and PCV13 can be administered concomitantly without compromising the antigen-specific immune response to either product. Vaccination with TIV within 6 months prior to enrollment was a study exclusion criterion. The TIV vaccine used in both studies was U.S. licensed Fluarix, manufactured by GSK. Each 0.5 mL dose is formulated to contain 15 µg HA of each of the 3 strains recommended for the 2007/2008 season: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004.

7.1 Study 6115A1-3001 (NCT00521586)

Title: A phase 3, randomized, double-blind trial to evaluate the safety, tolerability, and immunogenicity of Prevnar 13 when administered concomitantly with trivalent inactivated influenza vaccine (TIV) in healthy adults 50 to 59 years of age who are naïve to 23-valent pneumococcal polysaccharide vaccine and to evaluate the immune response of a second dose of Prevnar 13 administered 5 years after initial Prevnar 13 vaccination. Year 0 Report.

7.1.1 Study Design

This is a phase 3, randomized (1:1), double-blind, multicenter trial.

Table 33: Study 3001 Design

Subjects	Group	N (enrolled)	N (evaluable)	Vaccinations		
				Dose 1 (Day 1)	Dose 2 (Day 29-43)	Dose 3 (Year 5)
Healthy Adults Aged 50 to 59 Years Naïve to 23vPS	1	550	511	PCV13 + TIV	Placebo	PCV13
	2	550	511	Placebo + TIV	PCV13	PCV13
Total		1100	1022			

Source: 125324/262.0,m5.3.5.1.3, CSR-76160-protocol-amend, pages 44 (Table 16-1) and 56.

7.1.2 Study Objectives

The clinical study report submitted to the BLS includes data from Year 0 of this study (i.e. study start through 6-month follow-up telephone call). Data collected beyond Year 0 and pertaining to the secondary objectives above will be submitted in a subsequent clinical study report.

Primary objectives

1. To demonstrate that immune responses induced by TIV when administered concomitantly with PCV13 are non-inferior to the corresponding immune responses induced by TIV alone, as measured by the standard hemagglutination inhibition assay (HAI) for the A/H1, A/H3, and B vaccine strains 1 month after vaccination with TIV.

2. To demonstrate that the serotype-specific immune responses induced by PCV13 when administered concomitantly with TIV are non-inferior to the corresponding immune responses induced by PCV13 administered 1 month after TIV, as measured by

serotype-specific IgG concentrations 1 month after initial vaccination with PCV13 in a subset of subjects.

Secondary objectives

1. To evaluate the immune response to PCV13 before and after initial vaccination and the kinetics of the immune response to PCV13 for 5 years by serotype-specific OPA titers measured annually (years 1 to 5) in a subset of subjects.

2. To evaluate the immune response to re-vaccination with PCV13 administered 5 years after the initial PCV13 administration as measured by serotype-specific IgG concentrations in a subset of subjects 1 month after re-vaccination.

3. To evaluate the immune response to re-vaccination with PCV13 administered 5 years after the initial PCV13 vaccination as measured by serotype-specific OPA titers in a subset of subjects 1 month after re-vaccination.

Immunogenicity endpoints

The primary endpoints for TIV comparisons were the proportion of subjects who had at least a 4-fold increase in HAI titer (i.e. seroconverters/responders) for each influenza virus type or subtype from Day 1 to 28 to 57 days after TIV vaccination.

The primary endpoints for the pneumococcal comparisons were the serotype-specific pneumococcal IgG concentrations measured by ELISA 28 to 57 days after PCV13 vaccination in a subset of 562 subjects.

7.1.3 Populations Analyzed

Two analysis populations were defined for immunogenicity analyses at each of the two study doses. The all-available population included all subjects who had at least 1 valid and determinate assay result related to that vaccination. The evaluable immunogenicity population was identical to the evaluable immunogenicity population for cohort 2 of study 004, with exceptions: subjects in study 3001 had to be randomly assigned to a vaccine group, had to receive all year 0 study vaccinations, and had to have received the expected study concomitant vaccination (TIV).

7.1.4 Immunogenicity Results

Co-Primary Study Objective for TIV Strains: Proportion of Responders (Table 34)
For each influenza strain in TIV, the criterion for demonstrating non-inferiority of PCV13 + TIV compared to placebo + TIV (a co-primary study objective) was a lower limit of the 2-sided 95% CI for the difference in the proportions of subjects achieving at least a 4-fold increase in HAI titer (seroconversion) > -10%. This criterion was met by each of the 3 influenza strains in TIV.

Table 34. Study 6115A1-3001. Proportion of Subjects Achieving a ≥ 4-Fold Increase in HAI Titer for Concomitant Vaccine (TIV) Antigens After Dose 1 (Year 0); Vaccine Naïve Subjects Aged 50-59 Years. (Evaluable Immunogenicity Population)

	Vaccine Sequence (as Randomized)						Difference in Proportions [(PCV13+TIV) – (Placebo+TIV)]	
	Group 1 PCV13 + TIV N[a]=530			Group 2 Placebo + TIV N[a]=531				
Concomitant TIV HAIs	**n[b]**	**%**	**95% CI[c]**	**n[b]**	**%**	**95% CI[c]**	**%**	**95% CI[d]**
A/H1N1	445	84.0	80.6, 87.0	431	81.2	77.6, 84.4	2.8	-1.8, 7.4
A/H3N2	377	71.1	67.1, 75.0	369	69.5	65.4, 73.4	1.6	-3.9, 7.2
B	321	60.6	56.3, 64.8	320	60.3	56.0, 64.5	0.3	-5.6, 6.2

[a] N = number of subjects with a determinate antibody titer to the given concomitant vaccine antigen.
[b] n = Number of subjects who meet the pre-specified level for the given antigen.
[c] Exact 2-sided confidence interval based upon the observed proportion of subjects.
[d] Exact 2-sided CI for the difference in proportions, PCV13+TIV – Placebo+TIV, expressed as a percentage.
This table presents results from a co-primary study objective. Non-inferiority was met when the lower limit of the 2-sided 95% CI for the difference between groups [(PCV13+TIV) – (Placebo+TIV)] was > -10%.
Source: 125324/262.0,m5.3.5.1.4, CSR76160-report-body, page 50 (Table 9-2)

Co-Primary Study Objective for PCV13 Pneumococcal Serotypes: IgG GMCs 1 Month After Vaccination in a Subset of Subjects (Table 35)
For each of the PCV13 pneumococcal serotypes contained in PCV13, the criterion for demonstrating the non-inferiority of concomitant PCV13 + TIV followed by placebo one month later compared to concomitant placebo + TIV followed by PCV13 one month later (a co-primary study objective) was a lower limit of the 2-sided 95% CI for the GMC ratio > 0.5 (2-fold). Although this criterion was met for all serotypes, GMCs elicited by concomitant PCV13+TIV followed by placebo one month later were consistently about 60-70% of the GMCs achieved by concomitant placebo+TIV followed by PCV13 one month later.

Table 35. Study 6115A1-3001. Unadjusted Comparisons of Pneumococcal IgG GMCs (µg/mL) After PCV13+TIV[a] and Placebo+TIV/PCV13[b]; Vaccine Naïve Subjects Aged 50-59 Years (Evaluable Immunogenicity Population)

	Vaccine Sequence (as Randomized)						GMC Ratio [(PCV13+TIV) / (Placebo+TIV/PCV13)]	
	Post-Dose 1 PCV13+TIV[a]			Post-Dose 2 Placebo+TIV/PCV13[b]				
Serotype	n[c]	GMC	95% CI[d]	n[c]	GMC	95% CI[d]	Ratio[e]	95% CI[f]
1	292	4.1	3.4, 4.8	289	5.5	4.6, 6.5	0.74	0.58, 0.95
3	290	1.2	1.0, 1.3	288	1.5	1.3, 1.7	0.79	0.66, 0.93
4	290	2.4	2.0, 2.8	288	3.4	2.9, 4.0	0.69	0.55, 0.87
5	293	6.0	5.2, 7.1	289	7.2	6.1, 8.4	0.84	0.67, 1.05
6A	293	5.8	5.0, 6.6	288	6.7	5.7, 7.8	0.86	0.70, 1.06
6B	292	7.6	6.5, 8.8	289	10.1	8.6, 11.9	0.75	0.60, 0.93
7F	293	8.1	7.1, 9.4	289	10.6	9.1, 12.3	0.77	0.63, 0.95
9V	293	5.0	4.3, 5.7	289	7.0	6.1, 8.0	0.71	0.59, 0.86
14	294	10.8	9.0, 12.8	288	14.1	11.8, 16.7	0.77	0.60, 0.98
18C	293	9.7	8.3, 11.2	288	13.5	11.6, 15.7	0.72	0.58, 0.88
19A	294	16.8	14.8, 19.1	289	18.8	16.4, 21.7	0.89	0.74, 1.08
19F	291	6.1	5.2, 7.2	286	7.1	5.9, 8.6	0.86	0.67, 1.10
23F	294	7.2	6.1, 8.5	289	8.5	7.1, 10.3	0.84	0.66, 1.08

[a] Concomitant administration of PCV13 and TIV.
[b] Concomitant administration of placebo and TIV followed by administration of PCV13 one month later.
[c] n = number of subjects with a determinate IgG concentration elicited by the given serotype.
[d] CIs are back transformations of a CI based on Student t distribution for mean logarithm of concentrations.
[e] Ratio of GMCs for PCV13+TIV/Placebo to Placebo+TIV/PCV13 were calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13+TIV/Placebo – Placebo+TIV/PCV13).
This table presents results from a co-primary study objective in a subset of subjects . Non-inferiority was met when the lower limit of the 2-sided 95% CI for the GMC ratio was < 0.5.
Source: 125324/262.0,m5.3.5.1.4, CSR76160-report-body, page 59 (Table 9-7) and 125324/262.10, m1.11.3, Information Amendment page 1 (Table 1-1).

When the same comparisons were made using the GMC ratios and adjusting for covariates (i.e. current smoking status and pre-dose 1 value) in the supportive analysis, the non-inferiority criterion was met for all serotypes (data not shown).

Immune Responses Based on FDA Recommendations for Minimum Immunogenicity Response Among Adults < 65 Years of Age for New TIV Vaccines (Tables 34 and 36)

The lower limit of the 2-sided 95% CI for the proportion of subjects achieving at least a 4-fold increase in HAI titer exceeded 40% for each of the 3 TIV strains in both Group 1 and Group 2 (Table 34).

The lower limit of the 95% CI for the proportion of subjects achieving an HAI antibody titer ≥ 1:40 exceeded 70% for the two A strains in Group 1 and for each of the 3 TIV strains in Group 2 (Table 36). The lower limit of the 95% CI was 68.4% for the B strain in Group 1.

Table 36. Study 6115A1-3001. Proportion of Subjects Achieving an HAI Titer ≥ 40 After PCV13+TIV and after Placebo+TIV; Vaccine Naïve Subjects Aged 50-59 Years (Evaluable Immunogenicity Population)

	Vaccine Sequence (as Randomized)					
	Group1 PCV13 + TIV N[a]=530			Group 2 Placebo + TIV N[a]=531		
Concomitant TIV HAIs	**n[b]**	**%**	**95% CI[c]**	**n[b]**	**%**	**95% CI[c]**
A/H1N1	511	96.4	94.5, 97.8	515	97.0	95.2, 98.3
A/H3N2	523	98.7	97.3, 99.5	518	97.6	95.8, 98.7
B	384	72.5	**68.4**, 76.2	412	77.6	73.8, 81.1

[a] N = number of subjects with a determinate antibody titer to the given concomitant vaccine antigen.
[b] n = Number of subjects who meet the pre-specified level for the given antigen.
[c] Exact 2-sided confidence interval based upon the observed proportion of subjects.
This table represents descriptive data.
Source: 125324/262.0,m5.3.5.1.4, CSR76160-report-body, page 51 (Table 9-3)

Standard HAI GMTs after dose 1 are shown in Table 37.

Table 37. Study 6115A1-3001. Standard HAI GMTs From Pre-Dose 1 to Post-Dose 1; Vaccine Naïve Subjects Aged 50-59 Years (Evaluable Immunogenicity Population)

TIV HAIs	Randomized Vaccine Sequence	Sampling Time					
		Pre-dose 1			Post-dose 1		
		n[a]	GMT[b]	95% CI[c]	n[a]	GMT[b]	95% CI[c]
A/H1N1	**PCV13+TIV**	530	26	23, 29	530	332	301, 366
	Placebo+TIV	531	24	22, 27	531	331	298, 366
A/H3N2	**PCV13+TIV**	530	43	38, 50	530	443	400, 491
	Placebo+TIV	531	50	43, 57	531	478	427, 534
B	**PCV13+TIV**	530	14	13, 15	530	68	61, 76
	Placebo+TIV	531	15	14, 16	531	78	70, 87

[a] n = Number of subjects with valid and determinate assay results for the specified antigen at the given visit.
[b] GMTs were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
This table represents descriptive data.
Source: 125324/262.0,m5.3.5.1.4, CSR76160-report-body, page 53 (Table 9-4)

OPA Antibody Results

OPA testing was performed on a subset of 607 subjects. Subjects for the OPA analysis were selected from the subset of subjects included in the pneumococcal IgG analysis who had sufficient sera for OPA testing. If subjects in the IgG subset did not have sufficient sera for OPA testing, then additional subjects were selected consecutively from the randomly ordered subjects list.

The applicant provided a summary of OPA GMT ratios and the proportion of subjects achieving OPA lower limits of quantitation. The non-inferiority criterion defined for the

primary pneumococcal endpoint in this study and the statistical rules applied to the OPA analyses in studies 004 and 3005 were applied to the OPA analyses. These results are descriptive.

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month After Concomitantly Administered PCV13 and TIV Compared to 1 Month After PCV13 Administered Alone in a Subset of Subjects (Table 38)

For each of the 13 pneumococcal serotypes contained in PCV13, the criterion for demonstrating non-inferiority of concomitantly administered PCV13 + TIV compared to concomitantly administered placebo + TIV was a lower limit of the 2-sided 95% CI for the GMT ratio > 0.5 (2-fold). This criterion was met by 8 of the 13 vaccine serotypes; however, the lower limit of the 95% CI for the GMTs following PCV13+TIV were about 50-60% of the values achieved in the Placebo+TIV/PCV13 group. Serotypes 1, 5, 7F, 9V, and 19F failed to meet this non-inferiority criterion.

Table 38. Study 6115A1-3001. Pneumococcal OPA GMTs After PCV13+TIV[a] and After Placebo+TIV/PCV13[b]; Vaccine Naïve Subjects Aged 50-59 Years (Evaluable Immunogenicity Population)

	Vaccine Sequence (as Randomized)							
	Post-Dose 1 PCV13+TIV[a]			Post-Dose 2 Placebo+TIV/PCV13[b]			GMT Ratio [(PCV13+TIV) / (Placebo+TIV/PCV13)]	
Serotype	**n[c]**	**GMT**	**95% CI[d]**	**n[c]**	**GMT**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	289	150	123, 183	285	264	219, 319	0.6	**0.43**, **0.75**
3	280	61	52, 72	274	78	67, 91	0.8	0.63, **0.98**
4	280	1657	1403, 1956	282	2203	1868, 2598	0.8	0.60, **0.95**
5	273	100	77, 130	281	204	163, 255	0.5	**0.35**, **0.69**
6A	283	2160	1754, 2660	289	3157	2576, 3868	0.7	0.51, **0.91**
6B	279	2421	1983, 2955	286	3215	2637, 3918	0.8	0.57, 1.00
7F	268	1584	1251, 2005	281	2691	2193, 3302	0.6	**0.43**, **0.80**
9V	285	1053	813, 1363	285	1749	1383, 2211	0.6	**0.43**, **0.85**
14	284	1020	842, 1234	283	1554	1300, 1857	0.7	0.51, **0.85**
18C	279	1440	1141, 1818	285	1978	1593, 2455	0.7	0.53, 1.00
19A	281	777	660, 915	277	1022	880, 1186	0.8	0.61, **0.95**
19F	283	379	296, 486	283	625	496, 788	0.6	**0.43**, **0.85**
23F	271	382	292, 501	281	483	369, 631	0.8	0.54, 1.16

[a] PCV13 and TIV administered concomitantly.
[b] Concomitant administration of placebo and TIV followed by administration of PCV13 one month later.
[c] n = Number of subjects with a determinate IgG concentration elicited by the given serotype.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs for PCV13+TIV/Placebo to Placebo+TIV/PCV13 were calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13+TIV/Placebo – Placebo+TIV/PCV13).
This table represents descriptive data in a subset of subjects.
Source: 125324/262.7, m1.11.3, Efficacy Information Amendment – Clinical Supplemental Report, page 7 (Table 3-1) and 125324/262.9, m1.11.3 Efficacy Information Amendment – TIV OPA Analyses, page 2 (Table 1-1) and 125324/13, m5.3.5.1.3, Study 3001 Report Body Addendum, page 13 (Table 4-2).

Clinical Reviewer Note: pre-vaccination OPA GMTs (prior to receipt of PCV13) were not substantially different between the two study groups (data not shown).

7.2 Study 6115A1-3008 (NCT00492557)

Title: A phase 3, randomized, double-blind trial in Germany, the Netherlands, Belgium, and Hungary to evaluate the safety tolerability, and immunogenicity of PCV13 when administered concomitantly with TIV in adults aged ≥ 65 years who are naïve to 23vPS.

7.2.1 Study Design

This was a phase 3, parallel group, randomized (1:1), double-blind, multicenter trial in adults ≥ 65 years of age naïve to 23vPS.

Table 39. Study 6115A1-3008 design.

Group	N	Vaccination 1 (Day 1)	Vaccination 2 (Day 29 to 43 After Visit 1)
1	550	PCV13 + TIV	Placebo
2	550	Placebo + TIV	PCV13

Source: 125324/262.0,m5.3.5.1.4, CSR75180-report-body, page 26 (Table 11-1)

7.2.2 Study Objectives

Co-Primary objectives

1. To demonstrate that the immune responses induced by TIV when administered concomitantly with PCV13 are non-inferior to the immune responses induced by TIV alone, as measured by standard HAI for the A/H1N1, A/H3N2, and B vaccine strains 1 month after vaccination with TIV.
2. To demonstrate that the anti-pneumococcal immune responses induced by PCV13 when administered concomitantly with TIV are non-inferior to the corresponding immune responses induced by PCV13 administered 1 month after vaccination with TIV, as measured by serotype-specific IgG antibody concentrations in a subset of subjects.

7.2.3 Immunogenicity results

Co-Primary Study Objective: Proportion Achieving ≥ 4-fold increase in HAI Titer (Seroconversion) (Table 40)

For each influenza strain in TIV, the criterion for demonstrating non-inferiority of PCV13+TIV compared to placebo + TIV was a lower limit of the 2-sided 95% CI for the difference in proportions of subjects achieving at least a 4-fold increase in HAI titer (seroconversion) > -10%. This criterion was met by two of the three influenza strains in TIV; the lower limit of the 95% CI was -10.4% for the A/H2N1 strain.

Table 40. Study 6115A1-3008. Proportion of Subjects Achieving a ≥ 4-Fold Increase in HAI Titer for Concomitant Vaccine (TIV) Antigens After Dose 1 in 23vPS-Naïve Adults Aged ≥ 65 Years (Evaluable Immunogenicity Population

	Vaccine Sequence (as Randomized)								Difference in Proportions (PCV13+TIV/Placebo) minus Placebo+TIV/PCV13)	
	Group 1 PCV13 + TIV				Group 2 Placebo + TIV					
Concomitant TIV HAIs	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**%**	**95% CI[d]**
A/H1N1	548	440	80.3	76.7, 83.5	546	429	78.6	74.9, 81.9	1.7	-3.1, 6.5
A/H3N2	545	316	58.0	53.7, 62.2	545	341	62.6	58.4, 66.6	-4.6	**-10.4**, 1.3
B	548	286	52.2	47.9, 56.4	546	295	54.0	49.7, 58.3	-1.8	-7.8, 4.1

[a] N = number of subjects with a determinate antibody titer to the given concomitant vaccine antigen.
[b] n = Number of subjects who meet the pre-specified level for the given antigen.
[c] Exact 2-sided confidence interval based upon the observed proportion of subjects.
[d] Exact 2-sided CI for the difference in proportions, PCV13+TIV – Placebo+TIV, expressed as a percentage.
Non-inferiority was met when the lower limit of the 2-sided 95% for the difference between groups [(PCV13+TIV/Placebo) minus (Placebo+TIV/PCV13)] was greater than -10%.
Source: 125324/262.0,m5.3.5.1.4, CSR75180-report-body, page 50 (Table 9-3)

Co-Primary Study Objective in Subset of Subjects: Pneumococcal IgG GMC (Tables 41)

For each pneumococcal serotype contained in PCV13, the criterion for demonstrating non-inferiority of concomitant PCV13+TIV compared to PCV13 administered one month after concomitant placebo+TIV was a lower limit of the 95% CI for the GMC ratio > 0.5 (2-fold criterion). Responses were evaluated in the group that received concomitant PCV13 and TIV both after dose 1 (i.e., PCV13+TIV) and after dose 2 (i.e., placebo administered 1 month after concomitant PCV13+TIV). The responses measured 1 month after PCV13 when administered concomitantly with TIV were non-inferior to responses to PCV13 administered one month after concomitant placebo+TIV for 12 of the PCV13 pneumococcal serotypes (Table 41); the lower limit of the 95% CI for serotype 19F was 0.49.

Table 41. Study 6115A1-3008. Pneumococcal IgG GMCs (µg/mL) After PCV13+TIV[a] and After Placebo+TIV/PCV13[b], in 23vPS-Naïve Adults Aged ≥ 65 Years (Evaluable Immunogenicity Population)

	Vaccine Group (as Randomized)							
	Post-Dose 1 PCV13+TIV			Post-Dose 2 Placebo+TIV/PCV13			GMC Ratio [(PCV13+TIV) / (Placebo+TIV/PCV13)]	
Serotype	**n[c]**	**GMC[d]**	**95% CI**	**n[c]**	**GMC[d]**	**95% CI**	**Ratio[e]**	**95% CI[f]**
1	276	2.52	2.07, 3.06	270	3.20	0.26, 0.36	0.79	0.60, 1.04
3	272	1.08	0.94, 1.24	273	1.15	0.35, 0.46	0.94	0.78, 1.13
4	279	2.15	1.79, 2.60	278	3.24	0.17, 0.23	0.66	0.51, 0.87
5	253	4.74	4.08, 5.50	255	6.90	1.87, 2.30	0.69	0.55, 0.86
6A	272	4.61	4.00, 5.31	264	6.10	1.58, 1.98	0.76	0.61, 0.94
6B	278	6.24	5.27, 7.39	264	6.43	1.28, 1.68	0.97	0.75, 1.25
7F	273	7.63	6.50, 8.96	253	9.04	0.71, 0.95	0.84	0.67, 1.07
9V	250	4.97	4.19, 5.91	247	6.21	0.84, 1.09	0.80	0.63, 1.02
14	272	8.95	7.33, 10.95	277	12.44	1.45, 2.07	0.72	0.53, 0.97
18C	247	8.88	7.55, 10.45	261	11.07	0.92, 1.23	0.80	0.64, 1.01
19A	266	11.93	10.23, 13.92	255	17.10	2.54, 3.23	0.70	0.56, 0.87
19F	277	4.78	4.00, 5.71	276	7.39	1.11, 1.55	0.65	**0.49**, 0.85
23F	277	5.82	4.74, 7.14	265	6.11	0.81, 1.07	0.95	0.71, 1.27

[a] Concomitantly administered PCV13 and TIV.
[b] PCV13 administered one month after concomitantly administered placebo and TIV.
[c] n = Number of subjects with a determinate IgG concentration elicited by the given serotype.
[d] GMCs were calculated using all subjects with available data for the specified blood draw.
[e] GMC ratio calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures [(PCV13+TIV) – (Placebo+TIV/PCV13)].
This table presents results from a co-primary study objective in a subset of study subjects. Non-inferiority was met when the lower-limit of the 2-sided 95% CI for the GMC ratio was > 0.5.
Source: 125324/262.0,m5.3.5.1.4, CSR75180-report-body, page 57 (Table 9-7)

Additional Analyses:

Table 42. Study 6115A1-3008. Standard Hemagglutination Inhibition Assay (HAI) GMTs After PCV13+TIV[a] and Placebo+TIV[a] in 23vPS-Naïve Adults Aged ≥ 65 Years (Evaluable Immunogenicity Population)

Concomitant TIV HAIs	Vaccine Group (As Randomized)	Sampling Time					
		Pre-Dose 1			Post-Dose 1		
		n[b]	**GMT**	**95% CI[c]**	**n[b]**	**GMT**	**95% CI[c]**
A/H1N1	PCV13+TIV	548	21.6	19.9, 23.6	548	195.5	176.6, 216.4
	Placebo+TIV	547	22.5	20.5, 24.6	546	191.9	173.4, 212.5
A/H3N2	PCV13+TIV	545	62.9	55.8, 70.9	545	327.4	293.5, 365.2
	Placebo+TIV	546	65.3	57.5, 74.1	545	413.2	370.5, 460.8
B	PCV13+TIV	548	22.3	20.4, 24.3	548	90.4	81.6, 100.2
	Placebo+TIV	547	22.5	20.6, 24.6	546	88.5	79.8, 98.1

[a] Administered concomitantly.
[b] n = Number of subjects who meet the pre-specified level for the given antigen.
[c] Exact 2-sided confidence interval based upon the observed proportion of subjects.
[d] Exact 2-sided CI for the difference in proportions, PCV13+TIV – Placebo+TIV, expressed as a percentage.
This table represents descriptive data.
Source: 125324/262.0,m5.3.5.1.4, CSR75180-report-body, page 49 (Table 9-2)

Immune Responses Based on FDA Recommendations for Minimum Immunogenicity Response Among Adults ≥ 65 Years of Age for New TIV Vaccines (Tables 40 and 43)

The lower limit of the 2-sided 95% CI for the proportion of subjects achieving at least a 4-fold increase in HAI titer exceeded 30% for each of the 3 TIV strains in both Group 1 and Group 2 (Table 40).

The lower limit of the 95% CI for the proportion of subjects achieving an HAI antibody titer ≥ 1:40 exceeded 60% for each of the 3 TIV strains in both group 1 and group 2 (Table 43).

Table 43. Study 6115A1-3008. Proportion of Subjects Achieving HAI Titer ≥ 40 After PCV13+TIV and Placebo+TIV in23vPS-Naive Adults Aged ≥ 65 Years (Evaluable Immunogenicity Population)

	Vaccine Sequence (as Randomized)							
	Group1 PCV13 + TIV[a]				Group 2 Placebo + TIV[a]			
Concomitant TIV HAIs	N[b]	n[c]	%	95% CI[d]	N[b]	n[c]	%	95% CI[d]
A/H1N1	548	515	94.0	91.6, 95.8	546	514	94.1	91.8, 96.0
A/H3N2	545	526	96.5	94.6, 97.9	545	531	97.4	95.7, 98.6
B	548	449	81.9	78.5, 85.1	546	444	81.3	77.8, 84.5

[a] Administered concomitantly.
[b] N = number of subjects with a determinate antibody titer to the given concomitant vaccine antigen.
[c] n = Number of subjects who meet the pre-specified level for the given antigen.
[d] Exact 2-sided confidence interval based upon the observed proportion of subjects.
This table represents descriptive data.
Source: 125324/262.0,m5.3.5.1.4, CSR75180-report-body, page 51 (Table 9-4)

Post-Hoc Analyses of OPA Antibody Results
OPA testing was performed on a subset of 541 subjects, and OPA GMT ratios were provided. Subject selection and statistical analyses were identical to those described for study 3001. The non-inferiority criterion defined for the primary pneumococcal endpoint in this study and the statistical rules applied to the OPA analyses in studies 004 and 3005 were applied to the OPA analyses in study 3008. These results are descriptive.

PCV13 Pneumococcal Serotypes: OPA GMTs 1 Month After Concomitantly Administered PCV13 and TIV Compared to 1 Month After PCV13 Administered One Month After Concomitant Placebo and TIV in a Subset of Subjects (Table 44)
Non-inferiority was observed for 10 of the 13 vaccine serotype with regards to the OPA titers achieved following concomitant PCV13 + TIV compared to PCV13 administered 1 month after concomitant placebo + TIV (i.e., the lower limit of the 2-sided 95% CI for the GMT ratio was observed to be 0.5). With regards to these 10 serotypes, the lower limit of the 95% CI for the GMTs following PCV13+TIV was, however, 54 to 77% of the value achieved in the Placebo+TIV/PCV13 group. Non-inferiority was not observed for serotypes 4, 7F, and 9V.

Table 44. Study 6115A1-3008. Pneumococcal OPA GMTs After PCV13+TIV[a] and After Placebo+TIV/PCV13[b]; 23vPS-Naïve Subjects Aged ≥ 65Years (Evaluable Immunogenicity Population)

	Vaccine Sequence (as Randomized)						GMT Ratio [(PCV13+TIV) / (Placebo+TIV/PCV13)]	
	Post-Dose 1 PCV13+TIV[a]			Post-Dose 2 Placebo+TIV/PCV13[b]				
Serotype	**n[c]**	**GMT**	**95% CI[d]**	**n[c]**	**GMT**	**95% CI[d]**	**Ratio[e]**	**95% CI[f]**
1	256	88	71, 108	255	95	77, 118	0.9	0.68, 1.24
3	235	46	38, 56	237	51	42, 62	0.9	0.69, 1.20
4	247	997	766, 1296	245	1486	1175, 1880	0.7	**0.47**, **0.95**
5	245	124	97, 159	234	112	85, 146	1.1	0.77, 1.60
6A	250	1220	951, 1567	252	1597	1256, 2030	0.8	0.54, 1.08
6B	259	1564	1239, 1974	248	2017	1565, 2600	0.8	0.55, 1.09
7F	246	607	444, 829	248	835	620, 1124	0.7	**0.47**, 1.12
9V	247	477	349, 653	242	723	528, 989	0.7	**0.42**, 1.03
14	247	975	782, 1216	236	1088	858, 1379	0.9	0.65, 1.24
18C	250	1158	910, 1475	244	1415	1122, 1786	0.8	0.59, 1.14
19A	251	445	365, 542	247	539	428, 680	0.8	0.61, 1.12
19F	247	378	296, 484	242	467	361, 605	0.8	0.57, 1.16
23F	252	245	180, 332	242	295	218, 401	0.8	0.54, 1.27

[a] Concomitant administration of PCV13 and TIV.
[b] PCV13 administered one month after concomitant administration of placebo and TIV.
[c] n = Number of subjects with a determinate IgG concentration elicited by the given serotype.
[d] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[e] Ratio of GMTs for PCV13+TIV/Placebo to Placebo+TIV/PCV13 were calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
[f] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13+TIV/Placebo – Placebo+TIV/PCV13).
This table represents descriptive data in a subset of study subjects.
Source: 125324/262.7, m1.11.3, Efficacy Information Amendment – Clinical Supplemental Report, page 9 (Table 3-3) and 125324/262.9, m1.11.3 Efficacy Information Amendment – TIV OPA Analyses, page 3 (Table 1-2).

8.0 Safety

8.1 Clinical Studies

Overview/Design

The 6 clinical studies that supported the safety of PCV13 in adults are listed in Table 45 below and the differences in safety monitoring across these studies are highlighted. Four of the 6 studies (studies 6115A1-004, -3010, -3001 and -3008) were conducted in adults not previously vaccinated with Pneumovax 23 (23vPS) i.e. "vaccine-naïve" subjects. Two of the 6 studies (studies 6115A1-3005 and -3000) were conducted in adults who had previously received 23vPS i.e. "pre-immunized" subjects.

These 6 studies will subsequently be referred to, without the prefix 6115A1-, as:

- primary studies 004 and 3005 (immunogenicity and safety in naïve and pre-immunized ≥ 5 years ago, subjects respectively),
- supporting study 3000 (safety in the subject pre-immunized ≥3 years ago),
- concomitant vaccination studies 3001 and 3008 with trivalent inactivated influenza vaccine (TIV) in vaccine naïve subjects ages 50-59 and ≥65 years, respectively and
- sequential use study 3010 (PCV13/PCV13, PCV13/ 23vPS and 23vPS/PCV13).

All of the 6 clinical studies evaluated both the safety and immunogenicity of PCV13, except for study 3000, which was an open label safety study conducted in pre-immunized subjects. Three (3) of the 6 adult studies compared PCV13 with 23vPS. Because the vaccines were different in physical appearance, a modified double-blind design was used in these studies. The term "modified double-blind" indicates that the study staff dispensing and administering the vaccine were unblinded, but all other study personnel, including the principal investigator, were blinded. In particular, the individuals who evaluated subject safety, as well as the subject, were blinded.

Because the clinical study designs were varied, attempting to address differences in age and prior receipt of Pneumovax 23, it was not feasible to perform an integrated summary of all of the solicited and unsolicited local and systemic safety data across the 6 adult studies that would be clinically meaningful. Consequently, some individual study data is summarized and, where appropriate, study data is combined if study populations were similar, or compared across studies when clinically relevant. An integrated safety analysis was performed for serious adverse events including deaths.

Subjects were analyzed according to the vaccine actually received. All participants who received at least 1 dose of study vaccine were included in the safety population. Subjects lacking safety data for a proposed analysis were excluded from that analysis. Adverse events (AEs) were categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. The safety definitions and collection methods were, in general, consistent across all studies. Notable exceptions include the following: 1) did not collect data on use of medications to treat pain or fever in study 004; 2) did not routinely collect safety information between 6 months post-dose 1 and dose 2 in studies 3005 and 3010; and 3) no 6-month follow-up phone contact in study 3008.

8.1.1 Safety monitoring

The safety monitoring and collection of safety data to support this efficacy supplement were considered adequate. The 6 adult studies varied with respect to design and objectives; however, they all used standardized methods for collection of safety data. Safety parameters evaluated in each study included unsolicited adverse events (AEs) and pre-specified, solicited adverse events (local reactions at the injection site and systemic events). Solicited local reactions included pain, redness, swelling, and limitation of arm movement. Solicited systemic events included fever, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain. Data regarding medications taken to treat pain and medications taken to treat fever were also collected in all studies**,** except study 004.

Subjects were instructed to monitor these local and systemic reactions and events daily for 14 days after each vaccination (day 1 being the day of vaccination), and to record the information in electronic diary cards, "e-diaries", which were based on a personal digital assistant or equivalent technology. Information was collected for AEs that occurred from each clinic visit at which vaccine was administered through the post-vaccination visit, which was to take place 29 to 43 days after vaccination. Approximately 6 months after each vaccination, subjects were to be contacted by phone and were asked to report any newly diagnosed chronic medical conditions (including autoimmune and neuro-inflammatory diseases) and any serious adverse events that had occurred since the last study visit, and this information was to be recorded on the AE case report form

In studies 3001 and 3008 (concomitant administration with influenza vaccine), in which a second dose of test article was administered at visit 2, information was also collected for AEs that occurred from visit 2 through visit 3 (29 to 43 days after visit 2). At the 6-month follow-up phone contact (which was to take place 166 to 194 days after the last administration of test article), subjects were to report any newly diagnosed chronic medical conditions (including autoimmune and neuroinflammatory diseases) and any serious adverse events that had occurred since the last study visit, and this information was to be recorded on the AE case report form (CRF).

In studies 3010 and 3005, AEs occurring after vaccination 2 were recorded in the same manner as for vaccination 1 (i.e., all AEs were to be recorded at the visit approximately 1 month after vaccination 2, whereas only new medical conditions and SAEs were to be recorded at the 6-month follow-up contact after vaccination 2). Per protocol, any AEs or SAEs that occurred during the 6-month period between the 6-month follow-up phone contact after vaccination 1 and the study visit for vaccination 2 were not to be recorded. Thus serious adverse events such as invasive pneumococcal disease during this period, prior to receiving vaccine 2 in the sequence may not have been captured.

Local Reactions

PCV13 and 23vPS were administered by intramuscular (IM) injection in the deltoid muscle. Local reactions at the injection site, including pain, redness, swelling, and limitation of arm movement, were assessed daily for 14 days. In concomitant vaccine

studies 3001 and 3008, local reactions were assessed for the pneumococcal vaccine injection site only (PCV13 or placebo for PCV13), and not for the trivalent inactivated influenza vaccine (TIV) injection site.

Subjects who experienced pain at the injection site were to grade the intensity of the pain according to the following scale:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating, with inability to do usual activity.

Subjects were given a caliper to measure any redness or swelling at the injection site and were to record the largest diameter of each in caliper units (range: 1 to 21, or 21+; 1 caliper unit = 0.5 cm). In case a caliper measurement was between 2 values, the higher value was to be reported. For data summarization, the intensity of redness or swelling was categorized according to the following terms and scale:

Absent	No or minimal redness or swelling present, <2.5 cm (<5 caliper units)
Mild	2.5 to 5.0 cm (≥5 to ≤10 caliper units)
Moderate	5.1 to 10.0 cm (>10 to ≤20 caliper units)
Severe	>10.0 cm (>20 caliper units)

Subjects were to assess limitation of arm movement by responding to these questions:

Have you had any problems moving your arm today?	(Yes or No)
Could you move your arm above your head today?	(Yes or No)
Could you move your arm above your shoulder today?	(Yes or No)

For data summarization, limitation of arm movement was categorized as:

Absent	No limitation of arm movement
Mild	Some limitation of arm movement
Moderate	Unable to move arm above head, but able to move arm above shoulder
Severe	Unable to move arm above shoulder

Systemic Events

Subjects were to measure their oral temperature daily for 14 days, using the digital thermometer provided. Temperature was to be measured at bedtime and at any time that a fever was suspected, and the highest temperature for each day was recorded to one decimal place in the e-diary. Fever was defined as an oral temperature ≥38.0°C (≥100.4^{0}F). If fever was present on day 14, then on each subsequent day the subject was to record whether fever was still present (yes or no) until the fever resolved, and then to enter the date on which the fever resolved. For data summarization, fever was categorized according to the following terms and scale:

Absent	<100.4 ^{0}F (<38.0^{0}C)
Mild	100.4^{0}F to 101.1^{0}F (38.0^{0}C to 38.4^{0}C)
Moderate	101.2^{0}F to 102.0^{0}F (38.5^{0}C to 38.9^{0}C)
Severe	102.1F^0 to 104.0^{0}F (39.0^{0}C to 40.0^{0}C)
Potentially life threatening	>104.0^{0}F (>40.0^{0}C)

For each systemic event (chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain), subjects recorded in the e-diary whether or not they had experienced the event on that day (yes or no). Diarrhea was monitored as a systemic event in study 3000 only. No information regarding the intensity of systemic events was recorded, except in study 3000 (uncontrolled, pre-immunized study population) , in which most systemic events were to be rated by the subjects as mild, moderate, or severe, based on pre-specified scales. In all studies except study 004, subjects also recorded whether they had taken medication to treat pain and whether they had taken medication to treat fever (yes or no) on each day.

Systemic Event Grading and Capture in Safety Study 3000
Systemic events (fever, chills, fatigue, headache, vomiting, diarrhea, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain) were monitored daily by subjects from day 1 through day 14 after study vaccine administration and recorded in the e-diary.

Oral temperature was collected daily at bedtime for 14 days and at any time that fever (temperature ≥38.0°C [100.4°F]) was suspected during day 1 through day 14. Temperature was measured and recorded to 1 decimal place. In the event of a fever, temperature was collected daily until the fever had resolved (1 day of temperature <38.0°C [<100.4°F]).

Other systemic events that were assessed according to severity (mild, moderate, and severe) and categorized by a scale, and included, fatigue, headache, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain: mild was no interference with activity; moderate was some interference with activity; severe was prevents daily routine activity.

In addition, the use of antipyretic and pain medication to treat symptoms was collected from day 1 through day 14 after study vaccine administration. An end date was captured for any use of antipyretic and pain medication.

Safety Methods and Analysis
The Applicant summarize how the statistical analysis of safety was conducted in study 004 (controlled, vaccine naïve): For each type of local reaction (pain, redness, swelling, limitation of arm movement) and systemic event (including fever), the difference in incidence between vaccine groups cohort 1: PCV13 vs 23vPS) was calculated along with corresponding 95% confidence intervals and p-values, based on the method of Chan and Zhang.[22] The proportion of subjects reporting local reactions and systemic events on each day was also summarized, and the duration of each type of event was summarized using descriptive statistics. For cohort 1(age 60-64), the difference in incidence between the vaccine groups, 95% CIs on the difference, and corresponding p-values were determined using the method of Miettinen and Nurminen.[23]

For each type of local reaction and systemic event (including fever and use of medications to treat pain or fever), the percentage of subjects experiencing the event was summarized for each vaccine group. In analyses comparing 2 vaccine groups, the exact 2-sided 95% confidence intervals (CIs) on the difference in proportions between the groups, and the corresponding p-values, were calculated using the methodology of Chan and Zhang.[22]

In study 3010, data collected after vaccination 2 were compared among 3 vaccine sequences (PCV13/ PCV13, PCV13 /23vPS, 23vPS/ PCV13). In these analyses, the incidences were compared using a 2-sided Fisher exact test to derive an overall p-value (omnibus p-value) and p-values for pair-wise comparisons between the vaccine sequences. For each parameter, the results of the pairwise comparisons were considered valid only if the omnibus p-value was significant (<0.05). In addition, data were compared between vaccination 2 and vaccination 1, both between vaccine sequence groups (23vPS/1 PCV13 vaccination 2 vs PCV13 vaccination 1; PCV13/23vPS vaccination 2 vs 23vPS vaccination 1) and within the same vaccine sequence group (1 PCV13/ PCV13 vs PCV13). When the groups were independent, these comparisons were made using the methodology of Chan and Zhang (as described above). Within-group comparisons were made using the adjusted Wald 2-sided confidence interval for the difference in dependent proportions (PCV13/ PCV13 vaccination 2 minus PCV13/ PCV13 vaccination 1), expressed as a percentage; and a difference between vaccinations was considered significant if the 95% CI on the difference excluded zero.[22]

Unsolicited Adverse Events

AEs are summarized separately for each vaccination (ie, dose 1 and dose 2 in studies 3001 and 3008; vaccination 1 and vaccination 2 in studies 3010 and 3005), including events that occurred from administration of the vaccine through the day of the next study visit approximately 1 month later. AEs reported as occurring from the post-vaccination visit through the 6-month follow-up telephone contact (per protocol, only newly diagnosed medical conditions and SAEs) were also summarized separately. Summaries show, for each System Organ Class (SOC) and preferred term, the percentage of subjects in each vaccine group who experienced at least 1 event corresponding to the SOC or preferred term. The difference in the incidence of AEs between independent vaccine groups was assessed using exact 2-sided CIs and corresponding p-values based on methodology proposed by Miettinen and Nurminen.[23] For intragroup comparisons (ie, vaccination 1 versus vaccination 2 in the PCV13/ PCV13 vaccine group in studies 3005 and 3010), the difference in the incidence of AEs between the 2 vaccinations was evaluated using adjusted Wald 2-sided CIs for the difference in dependent proportions.

8.1.2 Populations Analyzed

Demographics: Gender, Age, Ethnicity, Underlying Medical Conditions and Conditions that Increase the Risk for Invasive Pneumococcal Disease (IPD)

Gender, Age and Ethnicity

The 6 studies to support the safety of PCV13 were conducted in developed world countries (US and Europe) and included 6198 male and female subjects aged 50- 93.1 years. The majority of the subjects who participated in the 6 safety studies, were Caucasian females. Across the studies, the median age for the vaccine naïve adults was 54 to 71.2 years and the median age for the "pre-immunized" subjects was 74.3-76 years.

PCV13 was administered to 5,667 adults:
-1,916 previously vaccinated with 23vPS at least 3 years prior and 3,751 naïve to 23vPS.
-2,616 adults were aged 50 to 64 years and 3,051 adults were 65 years and older.

The safety and tolerability of PCV13 in adults ≥65 years of age were also evaluated by examining data separately for 4 age subgroups within this population: subjects 65 to 69 years of age; 70 to74 years of age; 75 to 79 years of age; and ≥80 years of age.

Two studies (study 004 and 3010) assessed the safety of PCV13 in 23vPS unvaccinated adults aged 50-64 years. In both studies there were more females (53.5% to 61.8%) than males (38.2% to 46.5%). By races 94.2% to 97.0% of adults were White, 1.0% to 3.6% were Black or African-American, 0.0% to 1.4% were Asian, 0.0% to 1.0% were American Indian or Alaska Native, 0.0% to 0.2% were Native Hawaiian or Other Pacific Islander, and 0.0% to 1.4% were of 'Other' race. Between 2.0% and 3.1% of adults were Hispanic or Latino.

Two studies (3000 and 3005) assessed the safety of PCV13 in adults aged ≥68 years pre-vaccinated with 23vPS. In the first study with PCV13 there were 55.7% females and 44.3% males; in the other study which had 23vPS as a comparator there were 47.7% and 49.7% females and 50.3% and 52.3% males in each group. In the 2 studies by race, 95.9% to 97.8% were White, 1.5% to 2.6% were Black or African-American, 0.3% to 1.7% were Asian, 0.1% to 0.2% were American Indian or Alaska Native, 0.0% to 0.2% were Native Hawaiian or Other Pacific Islander, and 0.0% to 0.4% were of 'Other' race. Between 0.6% and 1.1% of adults were Hispanic or Latino.

Two studies (3001 and 3008) assessed the safety of PCV13 when administered concomitantly with trivalent inactivated influenza vaccine (TIV). The TIV utilized in both of these studies included the A/H1N1, A/H3N2, and B vaccine strains and the studies were conducted in the US (Sept 2007-Nov 2008) and Europe (Oct 2007-Feb 2008) in 23vPS unvaccinated adults. In study 3001 with adults aged 50-59 years there were more females (57.5%) than males (42.5%); in study 3008 with adults aged ≥65 years there were 50.2% females and 49.8% males. Among adults aged 50-59 years there was a higher percentage of Black or African-American (6.2%-7.5% across vaccine groups) compared to adults aged ≥65 years with 0.2% in each vaccine group. In these 2 studies by race, 91.1% to 99.3% were White, 0.2% to 7.5% were Black or African-American, 0.3% to 0.9% were Asian, 0.0% to 0.7% were American Indian or Alaska

Native, 0.0% to 0.4% were Native Hawaiian or Other Pacific Islander, and 0.2% to 0.9% were of 'Other' race. Between 4.0% and 4.8% of adults in the U.S. study were Hispanic or Latino; ethnicity data was not collected in the European study.

Underlying Medical Conditions

The study population included healthy adults as well as subjects with underlying diseases that overall provided an adequate representation of conditions found in this age demographic which included subjects ≥ 65 years. Please see the example of inclusion and exclusion criteria used in study 004 that is contained below. Data on smoking history within the past 6 months prior to study entry was also captured. However, specific information regarding duration of smoking and number of packs per day that a subject had smoked was not collected.

Medical Conditions that Increase the Risk for IPD

Medical histories were collected at baseline in all of the 6 primary studies. Subjects with Pre-existing chronic diseases or conditions could be included in the studies provided that the immune system was not impaired and that the condition was stable (defined as disease not requiring significant change in therapy or hospitalization because of worsening disease within 12 weeks before study entry). The medical monitors reviewed these summaries and identified conditions (by preferred terms) that, in their opinion, would likely place subjects at increased risk of pneumococcal disease ("high-risk" conditions). These terms were then grouped into 5 disease categories as follows: chronic cardiovascular diseases, chronic liver diseases including alcoholic liver disease and alcoholism, chronic pulmonary diseases, diabetes mellitus, and renal disorders. Subjects who had one or more of these conditions reported in their medical histories at study entry are referred to as "high-risk" subjects. Data for subjects with chronic liver disease were available for ≤8 subjects in any study; and only in studies 3000 and 3005 did subjects with renal disorders comprise ≥5% of the population. For the other high-risk categories (chronic cardiovascular diseases, diabetes mellitus, and pulmonary diseases), the number of subjects with these diagnoses was often low in studies that enrolled subjects <65 years of age, making interpretation of incidence data difficult. However, a larger representation of high-risk subjects can be found in the studies enrolling older adults (studies 3000, 3008, and 3005*)*. Using data for subjects who received PCV13 at vaccination 1, the percentage of subjects with any of the high-risk diagnoses was higher among subjects ≥65 years of age (36.9% to 55.5%; studies 3000, 3005, and 3008) than among younger subjects (17.1% to 26.4%; studies 004, 3001, and 3010).

Table 45 captures how the inclusion and exclusion criteria differed across the 6 safety studies according to major factors that could impact immunogenicity such as age and whether the subject had ever received 23vPS. There were some additional differences in inclusion and exclusion criteria. Below are examples of the inclusion and exclusion criteria used for the vaccine naïve subjects in study 004 vs the pre-immunized study populations in studies 3005 and 3000.

The following are examples of Inclusion/Exclusion Criteria utilized for vaccine naïve and pre-immunized subjects enrolled in the clinical studies (see Appendices for criteria on individual study inclusion and exclusion criteria)

Studies in Vaccine Naïve Subjects:
Study 004 (controlled, immunogenicity/safety, vaccine naïve age 50-64 yrs)
Subjects who satisfied the following inclusion criteria were eligible to participate in study 004 if all other qualifying criteria were met:

1. Determined by medical history, physical examination, and clinical judgment to be eligible for the study. Subjects with preexisting stable disease, defined as disease not requiring significant change in therapy* or hospitalization for worsening disease within 12 weeks before receipt of study vaccine, were eligible.
   ** Change in dose or therapy within a category (e.g., change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) was allowed. Change to new therapy categories (e.g., surgery, or addition of a new pharmacological class) was only allowed if it was not caused by worsening disease. A change to new therapy categories caused by worsening disease was considered significant.*
2. Able to complete an e-diary and follow study procedures in the opinion of the investigator.
3. Expected to be available for the duration of the trial.

Study 004 Exclusion Criteria
Subjects were excluded from participation in the study if they fulfilled any of the following criteria:

1. Previous vaccination with any licensed or experimental pneumococcal vaccine.
2. History of severe adverse reaction associated with a vaccine.
3. Receipt of any vaccine within 30 days before study vaccination (except influenza vaccine).
4. Vaccination with diphtheria-containing vaccines within 6 months before study vaccine administration or anticipated receipt of diphtheria-containing vaccine before study completion**.(**PCV13 contains *Diphtheria* CRM197 protein and high diphtheria antibody levels have been associated with increased local reactions).
5. Documented *Streptococcus pneumoniae* infection within the past 5 years.
6. Known or suspected hypersensitivity to any vaccine or vaccine components.
7. Known or suspected impairment of immunological function such as immunoglobulin class and subclass deficiencies, hematological malignancies, known HIV infection, collagen vascular disorders; and subjects receiving immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids. If systemic corticosteroids had been administered short term for treatment of an acute illness, subjects were excluded from vaccination until corticosteroid therapy had been discontinued for at least 1 month (30 days).
8. Serious chronic disorders including metastatic malignancy, severe chronic obstructive pulmonary disease requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion precluded the subject from participating in the study.
9. Poor or missing eyesight, requiring third-party support to read.

10. Receipt of any blood products, including immunoglobulin, within 6 months before study vaccine administration, or anticipation of receipt of blood products before study completion.
11. In the opinion of the investigator, unable to receive a vaccination in the deltoid muscle of either arm due to insufficient muscle mass.
12. Currently on anticoagulant therapy, or a history of bleeding diathesis that would contraindicate intramuscular (IM) injection.
13. Intent to receive any other investigational vaccine or agent from 30 days before study vaccine administration through the conclusion of the study.
14. Any medical condition that would, in the opinion of the investigator, interfere with the evaluation of the study objectives.

Studies in Pre-Immunized Subjects:

Study 3000 (uncontrolled, safety study in pre-immunized, age ≥68 yrs)

Additional Inclusion Criteria specific to study 3000

Subjects participated in the study if they satisfied all of the following inclusion criteria:

1. Male or female adult aged 68 years or older at the time of enrollment.
2. Documented vaccination with **1 or more doses** of 23vPS **at least 3 years** before study enrollment.
3. Determined by medical history, physical examination, and clinical judgment to be eligible for the study. Subjects with preexisting stable disease, defined as disease not requiring significant change in therapy* or hospitalization for worsening disease within 6 weeks before receipt of study vaccine, were eligible. * *Change in dose or therapy within a category (e.g., change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) was allowed. Change to new therapy categories(e.g., surgery, or addition of a new pharmacological class) was only allowed if it was not caused by worsening disease. A change to new therapy categories caused by worsening disease was considered significant.*

Additional Exclusion Criteria Specific to Study 3000

Subjects were excluded from participation in the study if they fulfilled any of the following criteria:

1. Residence in a nursing home, long-term care facility, or other institution or requirement of semiskilled nursing care. An ambulatory subject who was a resident of a retirement home or village was eligible for the trial.
2. Evidence of dementia or other severe cognitive impairment based on a Mini-Mental State Examination score of ≤21.
3. Currently on anticoagulant therapy or a history of bleeding diathesis that would contraindicate intramuscular (IM) injection (Note: antiplatelet drugs such as aspirin and clopidogrel were permitted).

****Collection of concomitant medications from visits 1 to 2 was added. At the follow-up phone-call (visit 3), collection of any newly diagnosed chronic medical conditions (including autoimmune and neuroinflammatory diseases) and any emergency room visits which meet the criteria of a serious adverse event (SAE) since visit 2 was added.*

Study 3005 (controlled, immunogenicity/safety in pre-immunized adults, age ≥ 70)
Inclusion/exclusion criteria were similar to study 3000 other than exceptions below.
Additional Inclusion Criteria specific for Study 3005:
Subjects who satisfied the following inclusion criteria were eligible to participate in this study if all other qualifying criteria were met:

1. Male or female adult aged 70 years or older at the time of enrollment.
2. Documented vaccination with **1 dose of 23vPS at least 5 years** before study enrollment.
3. Expected to be available for the duration of the trial (approximately 18 months).

Additional Exclusion Criteria specific for Study 3005
Subjects were ineligible to participate in this study if they received **more than 1 dose of 23vPS** before study enrollment or any prior pneumococcal conjugate vaccine.

8.1.3 Vaccine exposure and Disposition/ Study Completion
In the 6 primary studies, the safety populations comprise a total of 6198 subjects, of which 4213(68.0%) were naive to 23vPS and 1985 (32.0%) were pre-immunized. Overall, 49.4% of vaccinated subjects were between 50 and 64 years of age at enrollment (per protocol), and 50.6% were ≥65 years of age. Summarized by age (per protocol) at the time of enrollment, 2616 subjects (46.2%) vaccinated with PCV13 were between 50 and 64 years of age, while 3051 (53.8%) were ≥65 years of age; and among subjects vaccinated with 23vPS, 918 (66.0%) were between 60 and 64 years of age, while 473 (34.0%) were ≥65 years of age**.**

The safety of initial and subsequent study doses of pneumococcal vaccine administered 1 year apart was evaluated in studies 3010 and 3005. The number of subjects who received vaccination 2 in a sequence of 2 pneumococcal vaccines in these studies included a total of 551 subjects received PCV13/PCV13, 267 received PCV13/23vPS, and 627 received 23vPS/PCV13.

Studies in Vaccine Naive Subjects
The 4 primary studies that included naive subjects were studies 004, 3001, 3008, 3010). In each of these 4 studies in naive subjects, ≥99.1% of randomized subjects in each vaccine group received at least 1 dose of study vaccine**.**

- In studies 004 and 3010 (year 0 only), at least 98.0% of subjects in each group completed the 1-month postvaccination visit.
- In concomitant vaccination studies 3001 and 3008, at least 95.9% of subjects in each group completed the 1-month postvaccination visit after dose 2.
- Study 3008 did not have a 6-month follow-up telephone contact; in the 3 other studies, at least 94.0% of subjects in each group completed the 6-month follow-up contact.
- Note that in study 3001, the completion status for 3 subjects at the 6-month follow-up contact is shown as unknown; however, all 3 of these subjects actually completed the visit and this was corrected in a Clinical Data Report Errata.

8.1.4 Discontinuations

In study 004, 3.3% of subjects were withdrawn from the study after the 6-month follow-up contact for vaccination 1 but before the blood draw at year 1, while 94.5% of subjects completed the 1-year blood draw. In study 3010, 7.2% of subjects were withdrawn from the study after the 6-month follow-up contact for vaccination 1 but before vaccination 2. Overall, 90.3% of randomized subjects received vaccination 2, and 89.3% of subjects completed the 6-month follow-up phone contact after vaccination 2.

Across the 4 studies in vaccine naïve subjects, the most frequently reported reasons for study withdrawal were subject request and protocol violation. A total of 4 subjects died during the studies in **naive** subjects: 2 subjects (1 in each vaccine group) after receiving dose 2 in study 3008; 1 subject after receiving PCV13v+TIV in study 3001; and 1 subject after receiving PCV13 in study 004. Further details regarding deaths can be found in the **Table 47.** Deaths did not appear to be related to study vaccine.

A total of 5 subjects withdrew because of adverse events: 1 after receiving placebo+TIV in study 3001; 1 after receiving PCV13v+TIV/placebo in study 3008; 1 after receiving 23vPS in study 004; and 2 after receiving 23vPS in study 3010. Regarding withdrawals, there were no major imbalances across the treatment arms.

Studies in Pre-immunized Subjects

Disposition is summarized for the 2 studies in pre-immunized subjects: study 3000, in which all subjects received PCV13; and study 3005, in which subjects received either PCV13or 23vPS at vaccination 1. In both study 3000 and study 3005, ≥99.6% of randomized subjects in each vaccine group received at least 1 dose of study vaccine ≥99.1% of subjects in each group completed the 1-month post-vaccination visit, and ≥97.7% of subjects in each group completed the 6-month follow-up contact after vaccination 1. The most frequent reasons for withdrawal from the studies through the 6-month follow-up contact were subject request in study 3000 and protocol violations in study 3005.

In study 3005, 13.0% of subjects were withdrawn from the study after the 6-month follow-up contact for vaccination 1 but before vaccination 2. The most frequent reason for discontinuation at this point in the study was "other" (6.0%). Most of these subjects were withdrawn because they no longer qualified for the study, often because of deterioration in health or because of receipt of prohibited medications or blood products. Overall, 84.8% of randomized subjects received vaccination 2, and 84.1% of subjects completed the 6-month follow-up phone contact after vaccination 2. A total of 12 subjects died during the studies in pre-immunized subjects: 3 subjects after receiving PCV13 in study 3000, and a total of 9 subjects in study 3005 (4 after receiving PCV13, 4 after receiving 23vPS, and 1 after receiving PCV13/PCV13). None of the deaths appeared to be related to study vaccine. No subjects were withdrawn from study 3000 because of adverse events, while a total of 11 subjects were withdrawn from study 3005 because of adverse events: 4 after receiving PCV13v; 6 after receiving 23vPS; and 1 after receiving PCV13/PCV13. None of the adverse events leading to withdrawal were considered related to study vaccine.

A total of 16 subjects were withdrawn from the 6 clinical studies because of adverse events. Among the subjects withdrawn because of AEs, 6 had received PCV13, 9 had received 23vPS, and 1 had received only TIV+placebo. Among the 6 subjects who had received PCV13, 1 subject had received PCV13+TIV and 1 subject had received 2 doses of PCV13 1 year apart (PCV13v/PCV13). The type of AE most often leading to withdrawal was cancer (7 subjects). There were no withdrawals due to AEs in study 3000.

8.1.5 Serious Adverse Events (SAEs)

Deaths

Sixteen (16) subjects died during the 6 studies, 12 (0.21%) of the 5667 subjects who received PCV13 (or PCV13 +TIV) and 4 (0.29%) of the 1391 subjects who received 23vPS. None of the deaths appeared to be related to study vaccine. Most of the deaths (9 of the 16) occurred in study 3005, which enrolled only subjects who were ≥70 years of age.

In addition to the 16 deaths listed below which occurred in the 6 studies, a total of 15 deaths occurred in 2 supportive studies, 500 and 3009, which were not included in this safety review because they did not use the final commercial formulation of PCV13. In study 500, 9 subjects died after receiving PCV13; 4 subjects died after receiving 23vPS; and 1 subject died after receiving PCV13 followed by 23vPS 1 year later. One subject who had received PCV13/23vPS in study 500 died after receiving a third study vaccination (PCV13) in the follow-on study, 3009. Most of these deaths were the result of cardiovascular disease or cancer, and none of the deaths appeared to be related to study vaccine.

Serious adverse events (SAEs) reported at any time during the 6 studies are summarized in this section. Serious adverse events considered by the investigator to be at least possibly related to study vaccine were reported for 2 subjects and summarized as follows: Subject 3000-057-005613, a 78-year-old woman, developed Guillain-Barré syndrome on day 123 after vaccination with PCV13. Other possible risk factors included vaccination with influenza vaccine (on day 29 after vaccination with PCV13) and an infectious origin (varicella zoster was suspected because of eczema in the scapula area, but diagnosis was not confirmed). Follow-up information provided by the investigator indicated that this AE resolved.

Subject 3005-024-002310, an 81-year-old man, was diagnosed with idiopathic thrombocytopenic purpura 133 days after receiving vaccination 2 in the vaccination sequence 23vPS/PCV13 (vaccines administered 1 year apart). The subject was hospitalized with a platelet count of 3000/mL (normal range: 150,000 to 400,000/mL). He was treated with dexamethasone and was discharged 1 week later with a platelet count of 65,000/mL. Approximately 1 week later the subject was rehospitalized with a platelet count of 5000/mL. He began a regimen of weekly Rituxan® and methylprednisone and was discharged after 3 days with a platelet count of 29,000/mL. He was continued on the

weekly Rituxan and steroids for 3 more planned doses. The idiopathic thrombocytopenic purpura resolved approximately 3 months later (platelet count of 160,000/mL).

Serious adverse events occurring after an initial study vaccination of PCV13
Serious adverse events occurring within 1 month after an initial study vaccination of PCV 13 were reported at similar incidence across studies (in 0.2% to 1.1% of subjects), with no apparent differences related to subject age.

After an initial dose of PCV13, whether naïve or pre-immunized, the incidence of SAEs reported at the 6-month follow-up contact was slightly lower among subjects 50 to 59 years of age (1.2% to 1.8%) than among subjects 60 to 64 years of age (2.9% to 3.1%), and was highest among subjects ≥65 years of age (3.9% to 5.8%) Cardiac disorders and cerebrovascular (nervous system) events, neoplasms, respiratory disorders, and injuries occurred more frequently among subjects ≥65 years of age than among younger subjects.

Serious Adverse Events in study 004 : vaccine naïve subjects receiving PCV13 compared to 23vPS:

In cohort 1(age 60-64 yrs), SAEs occurring within approximately 1 month after vaccination were reported for 1 subject (0.2%) in the PCV13 group and for 2 subjects (0.5%) in the 23vPS group . Subject 005-000509, who received PCV13, was diagnosed with a hemangioma 32 days after study vaccination. In the 23vPS group, malignant melanoma, procedural pain, and cellulitis were reported for subject 012-001373, and subject 014-001606 had a myocardial infarction 29 days after vaccination. In cohort 2 (age 50-59 yrs), SAEs were reported for 2 subjects (0.5%). Subject 022-002515 was diagnosed with ovarian cancer; and subject 030-003124 developed cellulitis of the foot 5 days after vaccination.

In cohort 1 (age 60-64 yrs), SAEs were reported at the 6-month follow-up contact for 12 subjects (2.9%) who received PCV13 and for 10 subjects (2.4%) who received 23vPS . The most frequently reported types of SAEs were neoplasms benign, malignant, and unspecified, reported in 3 subjects (0.7%) in each vaccine group. In cohort 2 (age 50-59 yrs) SAEs were reported at the 6-month follow-up contact for 5 subjects (1.2%). Serious adverse events included conditions such as femur fracture, pancreatitis, bronchitis, meningioma and lymphadenectomy, and chest pain.

8.1.6 Local Reactions in the 6 Clinical Studies that supported Safety

Solicited Local Reactions After an Initial Study Vaccination of PCV13
The percentage of subjects reporting local reactions at the injection site within 14 days after an initial study vaccination of PCV13 is summarized in **Table 45** for each of the 6 clinical studies that supported safety. The table compares PCV13 reactogenicity across the various age groups enrolled (50 to 59 years, 60 to 64 years, and ≥65 years of age) and between pre-immunized subjects (studies 3000 and 3005) and vaccine naïve subjects. In studies 3001 and 3008, for each type of local reaction (redness, swelling, pain, and

limitation of arm movement), the percentage of subjects reporting the reaction at the PCV13 injection site after administration of PCV13+TIV was similar to the percentage of subjects reporting the reaction after administration of PCV13 alone. Therefore, Table 45 below includes pooled data for local reactions reported after dose 1 for subjects in the PCV13 + TIV/placebo group and after dose 2 for subjects in the placebo + TIV/ PCV13 group. The TIV injection site was not evaluated. For studies 3005 and 3010, the table includes data for vaccination 1 only.

Table 45 shows that the incidence of redness reported after an initial study vaccination of PCV13 ranged from 10.8% to 20.2% across the 6 studies, with no consistent differences among the age groups or between naive and pre-immunized subjects. In each of the 6 studies, most reports were mild, and the incidence of severe redness was ≤1.7%. Similar results were observed for swelling at the injection site: Across studies, the incidence of swelling ranged from 10.0% and 21.7%; most reports were mild; and in each study severe swelling was reported by ≤0.6% of subjects receiving an initial vaccination of PCV13. The incidence of pain was higher among subjects <65 years of age (ranging from 69.2% to 88.8%) than among subjects ≥65 years of age (41.7% to 51.7%). The incidence of moderate pain ranged from 20.1% to 40.1% among subjects <65 years of age and from 7.5% to 17.2% among subjects ≥65 years of age. Severe pain was reported most frequently among subjects 50 to 59 years of age (3.6% to 4.5%).

Similarly, the incidence of limitation of arm movement decreased with increasing age, being 39.1% to 40.7% among subjects 50 to 59 years of age, 23.5% to 28.5% among subjects 60 to 64 years of age, and 10.5% to 16.2% among subjects ≥65 years of age. Limitation of arm movement was most frequently reported as mild, and was reported as severe in ≤3.1% of subjects in any study.

Because of variations in the incidence of local reactions across age groups, the effects of vaccination status on reactogenicity can be evaluated by comparing data for pre-immunized subjects (studies 3000 and 3005, in subjects ≥68 years of age) with data for naive subjects ≥65 years of age (study 3008). However, the pooled subjects in the comparator group from study 3008 consisted of some subjects who were concomitantly receiving influenza vaccine which the Applicant states did not increase the local reactogenicity profile. As can be seen in Table 45, redness, swelling, and limitation of arm movement were reported at similar incidence in these studies. Pain was reported somewhat more often among pre-immunized subjects (51.0% to 51.7% of subjects) than among naïve subjects (41.7%).

Table 45 Local Reactions at 14 Days Post initial PCV13 dose

Table 2-1: Subjects Reporting Local Reactions Within 14 Days After an Initial Study Vaccination of 13vPnC, by Immunization Status and Age

	Naive to 23vPS					Preimmunized With 23vPS	
Study Number	**3001[a]**	**004**	**004**	**3010[b]**	**3008[a]**	**3000**	**3005[b]**
Age per Protocol (years)	**50-59 y (%)**	**50-59 y (%)**	**60-64 y (%)**	**60-64 y (%)**	**≥65 y (%)**	**≥68 y (%)**	**≥70 y (%)**
Local Reaction							
Redness[c]							
Any	14.3	15.8	20.2	12.2	14.4	14.3	10.8
Mild	13.1	15.2	15.9	8.3	12.1	12.6	9.5
Moderate	4.9	5.0	8.6	6.4	6.1	6.5	4.7
Severe	0.8	0.7	1.7	1.2	0.8	1.1	1.7
Swelling[c]							
Any	16.6	21.7	19.3	10.0	12.0	12.8	10.4
Mild	14.8	20.6	15.6	8.2	10.0	10.9	8.9
Moderate	6.1	4.3	8.2	3.8	4.6	5.5	4.0
Severe	0.4	0.0	0.6	0.0	0.1	0.6	0.0
Pain[d]							
Any	85.7	88.8	80.1	69.2	41.7	51.0	51.7
Mild	82.5	85.9	78.6	66.1	36.1	49.4	50.1
Moderate	40.1	39.5	23.3	20.1	17.2	9.0	7.5
Severe	4.5	3.6	1.7	2.3	2.0	0.2	1.3
Limitation of arm movement[e]							
Any	39.1	40.7	28.5	23.5	14.4	16.2	10.5
Mild	36.9	38.6	26.9	22.7	13.2	14.8	10.3
Moderate	5.2	2.9	2.2	1.2	1.2	1.6	0.3
Severe	3.1	2.9	1.7	1.1	1.6	1.6	0.7

Abbreviation: y = years.

a. For studies 3001 and 3008, percentages are based on pooled data from dose 1 for the 13vPnC+TIV/placebo sequence group and dose 2 for the placebo+TIV/13vPnC group.

b. For studies 3005 and 3010, data are shown for vaccination 1 (year 0) only.

c. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.

d. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.

e. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Program ID: Study 6115A1-Adult_ISS_EU/CP SAF_LR_SUM.SAS. Runtime ID: 12AUG2010 09:04

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Solicited Local Reactions in Vaccine Naive Subjects

In study 004, the percentage of subjects reporting local reactions within 14 days after an initial study vaccination was slightly higher in the PCV13 group than in the 23vPS group, respectively, for redness (20.2%, 14.2%), swelling (19.3%, 13.1%), and pain (80.1%, 73.4%), although the differences between groups were not statistically significant (Table 46)**.** The percentage of subjects reporting limitation of arm movement was similar in the PCV13 and 23vPS groups (28.5%, 30.8%, respectively). For all 4 reaction types, the majority of reports were mild. The incidence of mild pain was statistically significantly higher in the PCV13 (78.6%) than in the 23vPS group (68.6%) (p=0.005), while the incidence of severe pain was statistically significantly higher in the 23vPS group (8.6%) than in the PCV13 group (1.7%) (p=0.003). For the other 3 reaction types, severe reactions were reported by ≤4.3% of subjects in either vaccine group.

In study 3010, local reactions were reported at similar incidence in the PCV13 and 23vPS groups, respectively, for redness (12.2%, 11.2%), swelling (10.0%, 10.4%), and limitation of arm movement (23.5%, 28.2%) (see Table 46 below). Pain was reported more frequently by subjects receiving PCV13 than among those vaccinated with 23vPS, both for any pain (69.2%, 58.3%; p=0.014) and for mild pain (66.1%, 52.9%; p=0.004), although the incidences of moderate pain and severe pain were similar between the 2 groups. For each of the 4 types of local reactions, the incidence of severe reports was ≤2.3% in each vaccine group.

Table 46 Local Reactions within 14 days of Initial Study Vaccine

Table 2-2: Subjects Reporting Local Reactions Within 14 Days After an Initial Study Vaccination - Comparison of 13vPnC and 23vPS (Subjects Naive to 23vPS, 60-64 Years of Age)

	Study 004					Study 3010				
Local Reaction	13vPnC %	23vPS %	Difference[a]	(95% CI[b])	p-Value[b]	13vPnC %	23vPS %	Difference[a]	(95% CI[b])	p-Value[b]
Redness[c]										
Any	20.2	14.2	6.0	(-1.6, 13.7)	0.123	12.2	11.2	1.0	(-6.2, 7.4)	0.808
Mild	15.9	11.2	4.6	(-2.4, 11.7)	0.193	8.3	9.7	-1.4	(-8.2, 4.3)	0.637
Moderate	8.6	4.9	3.7	(-1.6, 9.3)	0.169	6.4	3.9	2.5	(-2.8, 7.0)	0.353
Severe	1.7	0.0	1.7	(-0.4, 4.8)	0.095	1.2	0.8	0.4	(-3.1, 2.8)	0.892
Swelling[c]										
Any	19.3	13.1	6.2	(-1.2, 13.7)	0.103	10.0	10.4	-0.4	(-7.3, 5.7)	0.931
Mild	15.6	10.1	5.6	(-1.2, 12.5)	0.120	8.2	6.1	2.1	(-3.8, 7.2)	0.495
Moderate	8.2	4.4	3.7	(-1.4, 9.2)	0.150	3.8	7.6	-3.8	(-9.8, 1.2)	0.140
Severe	0.6	1.1	-0.5	(-3.4, 2.1)	0.689	0.0	0.0	0.0	(-2.9, 1.6)	>.99
Pain[d]										
Any	80.1	73.4	6.6	(-0.1, 13.3)	0.052	69.2	58.3	10.9	(2.2, 19.7)	0.014
Mild	78.6	68.6	10.0	(3.0, 17.0)	0.005	66.1	52.9	13.2	(4.1, 22.2)	0.004
Moderate	23.3	30.0	-6.7	(-15.2, 1.8)	0.125	20.1	21.7	-1.6	(-10.2, 6.5)	0.708
Severe	1.7	8.6	-6.9	(-12.0, -2.1)	0.003	2.3	0.8	1.5	(-2.1, 4.4)	0.338
Limitation of arm movement[e]										
Any	28.5	30.8	-2.3	(-11.1, 6.5)	0.633	23.5	28.2	-4.6	(-13.8, 4.1)	0.311
Mild	26.9	29.3	-2.4	(-11.2, 6.2)	0.609	22.7	26.1	-3.3	(-12.4, 5.2)	0.458
Moderate	2.2	3.8	-1.6	(-5.8, 2.2)	0.536	1.2	3.1	-2.0	(-6.7, 1.1)	0.297
Severe	1.7	4.3	-2.7	(-6.8, 1.0)	0.147	1.1	2.3	-1.2	(-5.5, 1.6)	0.414

Table 46 Local Reactions within 14 days of Initial Study Vaccine (con't)

Table 2-2: Subjects Reporting Local Reactions Within 14 Days After an Initial Study Vaccination - Comparison of 13vPnC and 23vPS (Subjects Naive to 23vPS, 60-64 Years of Age)

	Study 004					Study 3010				
Local Reaction	13vPnC %	23vPS %	Difference[a]	(95% CI[b])	p-Value[b]	13vPnC %	23vPS %	Difference[a]	(95% CI[b])	p-Value[b]

a. Difference in proportions, expressed as a percentage.
b. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, 13vPnC – 23vPS, expressed as a percentage.
c. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
d. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
e. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Program ID: Study 6115A1-Adult_ISS_EU/CP SAF_LR_SUM_004_3010.SAS. Runtime ID: 03AUG2010 22:50
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/ISS/Reports, Tables, and Figures/Safety_Locals.zip/saf_lr_sum_004_3010.htm

Solicited Local Reactions : PCV13 compared to 23vPS in Pre-Immunized Elderly

Table 47 provides local reactogenicity information to consider when weighing the benefits and risks regarding re-vaccination of subjects who were pre-immunized in the past with 23vPS. Benefit of the vaccine regarding immune responsiveness should be weighed against the adverse event profile.

Study 3005 (≥ 70 yrs) used a dosing interval of **≥ 5** yrs to evaluate:
23vPS - 23vPS compared to 23vPS - PCV13

Study 3000 (≥68 yrs) used the dosing interval of ≥ 3yrs was an uncontrolled study and evaluated: 23vPS - PCV13

Study 004 (50-64 yrs) provides data for younger cohorts using a **3-4.5 year** interval between dosing and evaluated:
PCV13- PCV13 compared to 23vPS -PCV13 compared to 23vPS - 23vPS

Study 3010 (60-64yrs) provides data for younger cohorts using the **1 year** interval between dosing and evaluated:
PCV13- PCV13 compared to 23vPS - PCV13 compared to PCV13 - 23vPS

In subjects ≥70 years of age who had previously received 23vPS at least 5 years before enrollment (study 3005), the incidences of redness, swelling, and limitation of arm movement were statistically significantly higher after an initial study vaccination of 23vPS than after an initial study vaccination of PCV13 ($p<0.001$).

For these 3 reaction types, the differences between vaccine groups were also statistically significant at each severity level ($p<0.05$), except for mild redness (Table 47). The incidence of any pain was higher in the 23vPS group (58.5%) than in the 13vPnC group (51.7%), although the difference between the groups did not reach statistical significance ($p=0.062$). The incidence of moderate pain was significantly higher after administration of 23vPS (23.6%) than after PCV13v (7.5%) ($p<0.001$), while mild pain and severe pain were reported at similar incidence in the 2 groups. For each of the 4 types of local reactions, most reports were mild, and the incidence of severe reports was ≤4.8% in each vaccine group.

Table 47 Local Reactions Within 14 days after Initial Study vaccine

Table 2-3: Subjects Reporting Local Reactions Within 14 Days After an Initial Study Vaccination – Comparison of 13vPnC and 23vPS (Subjects Preimmunized With 23vPS, ≥70 Years of Age; Study 3005)

	Vaccine Group (as Administered)										
	13vPnC				23vPS						
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])	p-Value[e]
Redness[f]											
Any	306	33	10.8	(7.5, 14.8)	324	72	22.2	(17.8, 27.1)	-11.4	(-17.3, -5.6)	<.001
Mild	304	29	9.5	(6.5, 13.4)	311	42	13.5	(9.9, 17.8)	-4.0	(-9.1, 1.1)	0.129
Moderate	301	14	4.7	(2.6, 7.7)	314	36	11.5	(8.2, 15.5)	-6.8	(-11.3, -2.3)	0.002
Severe	299	5	1.7	(0.5, 3.9)	310	15	4.8	(2.7, 7.9)	-3.2	(-6.3, -0.3)	0.028
Swelling[f]											
Any	307	32	10.4	(7.2, 14.4)	333	77	23.1	(18.7, 28.0)	-12.7	(-18.5, -7.0)	<.001
Mild	305	27	8.9	(5.9, 12.6)	315	44	14.0	(10.3, 18.3)	-5.1	(-10.2, -0.1)	0.048
Moderate	299	12	4.0	(2.1, 6.9)	323	44	13.6	(10.1, 17.9)	-9.6	(-14.2, -5.1)	<.001
Severe	297	0	0.0	(0.0, 1.2)	310	15	4.8	(2.7, 7.9)	-4.8	(-7.9, -2.7)	<.001
Pain[g]											
Any	362	187	51.7	(46.4, 56.9)	383	224	58.5	(53.4, 63.5)	-6.8	(-14.0, 0.4)	0.062
Mild	359	180	50.1	(44.8, 55.4)	377	204	54.1	(48.9, 59.2)	-4.0	(-11.3, 3.3)	0.284
Moderate	306	23	7.5	(4.8, 11.1)	330	78	23.6	(19.2, 28.6)	-16.1	(-21.7, -10.6)	<.001
Severe	299	4	1.3	(0.4, 3.4)	306	7	2.3	(0.9, 4.7)	-0.9	(-3.5, 1.4)	0.539
Limitation of arm movement[h]											
Any	313	33	10.5	(7.4, 14.5)	326	90	27.6	(22.8, 32.8)	-17.1	(-23.1, -11.1)	<.001
Mild	312	32	10.3	(7.1, 14.2)	322	81	25.2	(20.5, 30.3)	-14.9	(-20.8, -9.0)	<.001
Moderate	297	1	0.3	(0.0, 1.9)	303	8	2.6	(1.1, 5.1)	-2.3	(-4.8, -0.4)	0.020
Severe	298	2	0.7	(0.1, 2.4)	305	9	3.0	(1.4, 5.5)	-2.3	(-4.9, -0.1)	0.042

Note: Data presented are from the vaccination 1 safety population.

a. N = number of subjects with known values.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. Difference in proportions, [13vPnC] – [23vPS], expressed as a percentage.
e. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, [13vPnC] – [23vPS], expressed as a percentage.
f. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
g. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
h. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Program ID: Study 6115A1-3005-WW/CP SAF_LR_WITHIN.SAS. Runtime ID: 01AUG2010 21:23
Source: Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/3005/Reports, Tables, and Figures/Safety_Locals/Safety_Locals_Final.zip/saf_lr_sum_v1.htm (modified)

The safety of the vaccine schedule of PCV13 followed by a booster dose of 23vPS at 1 year later was evaluated in adults aged 60 - 64 years in study 3010. The immune response data will also need to be considered to see if there is value in giving PCV13 - 23vPS on a 1 yr. or other schedule (3-4.5 years) compared to just waiting until age 65 yrs to administer 23vPS (see Table 48 below).

Comparisons Between Subsequent Vaccinations of PCV13 or 23vPS

Table 48 provides local reactogenicity information to consider when weighing the benefits and risks regarding whether to re-vaccinate with either PCV13 or 23vPS in

subjects who initially received a dose of PCV 13 or 23vPS. Schedules of vaccine doses separated by a 1 year interval that were evaluated in this study included:
PCV13 / PCV13, PCV13 / 23vPS and 23vPS/ PCV13. Benefit of the vaccine regarding immune responsiveness should be weighed against the adverse event profile.

In study 3010, the incidence of local reactions reported after subsequent study vaccinations **(vaccination 2)** was also compared among the 3 vaccine groups, and pairwise comparisons were made between the groups as follows:

PCV13 / PCV13	versus	PCV13 / 23vPS
PCV13 / PCV13	versus	23vPS / PCV13
PCV13 / 23vPS	versus	23vPS / PCV13

After vaccination 2, for <u>each of the 4 types of local reactions</u>, the incidence was highest in the PCV13/23vPS vaccine group and lowest in the 23vPS/ PCV13 group (see Table 48 below. In pairwise comparisons, the incidence of each type of reaction was <u>statistically significantly higher</u> in the PCV13/23vPS vaccine group than in either the PCV13/ PCV13 group or the 23vPS/ PCV13 group. Each of the 4 types of local reactions was reported more frequently after administration of PCV13/ PCV13 than after 23vPS/ PCV13, although the differences between the groups were **statistically significant** only for redness and for swelling. In all 3 groups, most reports of local reactions after vaccination 2 were mild. **Severe reactions** were reported most frequently in the PCV13/23vPS group, ranging from 6.1% for severe swelling to 12.9% for severe pain. For all 4 reaction types, the lowest incidence of severe reports was observed in the 23vPS/ PCV13 group (0.0% for severe redness and severe swelling; 0.9% for severe pain; and 1.7% for severe limitation of arm movement).

Table 48 Local Reactions within 14 days after Vaccination 2

Table 2-7: Subjects Reporting Local Reactions Within 14 Days After Vaccination 2 (Subjects Naive to 23vPS, 60-64 Years of Age; Study 3010)

	Vaccine Sequence (as Administered)										
	13vPnC/13vPnC			13vPnC/23vPS			23vPS/13vPnC				Omnibus
Local Reaction	N[a]	n[b]	%	N[a]	n[b]	%	N[a]	n[b]	%	p-Values[c]	p-Value[d]
Redness[e]											
Any	86	11	12.8	151	42	27.8	115	5	4.3	0.009, 0.036, <.001	<.001
Mild	83	6	7.2	144	28	19.4	115	5	4.3	0.012, 0.531, <.001	<.001
Moderate	83	6	7.2	138	17	12.3	115	1	0.9	0.263, 0.022, <.001	<.001
Severe	83	2	2.4	131	9	6.9	115	0	0.0	0.209, 0.174, 0.004	0.006
Swelling[e]											
Any	86	12	14.0	155	40	25.8	119	6	5.0	0.034, 0.043, <.001	<.001
Mild	85	9	10.6	149	30	20.1	119	6	5.0	0.069, 0.175, <.001	<.001
Moderate	82	5	6.1	138	17	12.3	116	1	0.9	0.167, 0.084, <.001	<.001
Severe	82	1	1.2	132	8	6.1	115	0	0.0	0.158, 0.416, 0.008	0.007
Pain[f]											
Any	129	97	75.2	231	198	85.7	169	118	69.8	0.015, 0.362, <.001	<.001
Mild	123	89	72.4	205	161	78.5	166	113	68.1	0.229, 0.440, 0.024	0.072
Moderate	91	22	24.2	176	87	49.4	129	23	17.8	<.001, 0.309, <.001	<.001
Severe	83	2	2.4	140	18	12.9	116	1	0.9	0.007, 0.572, <.001	<.001
Limitation of arm movement[g]											
Any	93	26	28.0	178	95	53.4	130	24	18.5	<.001, 0.105, <.001	<.001
Mild	92	25	27.2	171	81	47.4	130	22	16.9	0.002, 0.069, <.001	<.001
Moderate	83	3	3.6	134	14	10.4	115	0	0.0	0.075, 0.072, <.001	<.001
Severe	82	1	1.2	135	11	8.1	115	2	1.7	0.033, >.99, 0.024	0.018

Note: Data presented are from the vaccination 2 safety population.

a. N = number of subjects with known values.
b. n = Number of subjects with the specified characteristic.
c. Fisher exact test, 2-sided. Pairwise comparison (13vPnC/13vPnC vs 13vPnC/23vPS, 13vPnC/13vPnC vs 23vPS/13vPnC, 13vPnC/23vPS vs 23vPS/13vPnC).
d. Fisher exact test, 2-sided, for comparison of all 3 vaccine groups.
e. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
f. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
g. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Program ID: Study 6115A1-3010-WW/CP SAF_LR_COMP.SAS. Runtime ID: 09FEB2010 22:36
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/3010/Reports, Tables, and Figures/Safety_Locals/Locals_09FEB2010.zip/saf_lr_comp_d2.htm (modified)

Concomitant Administration of PCV13/ Trivalent Influenza Vaccine (TIV)

Two studies (3001 and 3008) assessed the safety of PCV13 when administered concomitantly with trivalent inactivated influenza vaccine (TIV). The TIV utilized in both of these studies included the A/H1N1, A/H3N2, and B vaccine strains and the studies were conducted in the US (study 3001 from Sept 2007-Nov 2008) and Europe (study 3008 from Oct 2007-Feb 2008) in 23vPS unvaccinated adults.

Local Reactions After Concomitant Administration of PCV13 and TIV

The concomitant administration of PCV13 and trivalent inactivated influenza vaccine (TIV) was evaluated in 2 studies. Both studies were conducted in vaccine naive subjects; **study 3001** enrolled subjects **50 to 59** years of age, and **study 3008** enrolled subjects **≥65 years** of age. Subjects received 2 doses of study vaccine 1 month apart, administered

as PCV13 +TIV/placebo or placebo+TIV/PCV13. **Local reactions were evaluated for the PCV13 injection site only**; local reactions at the TIV injection site were not evaluated. The analyses of primary interest compared data for local reactions reported after PCV13 administered concomitantly with TIV (dose 1 for the 13vPnC+TIV/placebo group) with data collected after administration of PCV13 alone (dose 2 for the placebo+TIV/ PCV13 group). The results from both studies demonstrate that, for each type of local reaction (redness, swelling, pain, and limitation of arm movement), the percentage of subjects reporting the reaction at the PCV13 injection site after administration of PCV13 + TIV was similar to the percentage of subjects reporting the reaction after administration of PCV13 alone.

In **study 3001(age 50-59 years),** all 4 types of local reactions were reported at similar frequencies after PCV13 + TIV and after PCV13 alone **(Table 49).** For each reaction type, the difference in incidence between groups was 6.8 percentage points or less, and none of the differences were statistically significant. Similarly, in analyses of local reactions by severity (mild, moderate, severe), there were no statistically significant differences between the groups, except for the incidence of mild limitation of arm movement, which was statistically higher after PCV13 alone (41.1%) than after PCV13+TIV (32.6%). For all 4 reaction types, in each vaccine group, most reports were of mild intensity, and ≤4.8% of reports were severe.

In **study 3008 (age ≥ 65 yrs)** the results were similar. For each type of reaction and at each intensity level, the difference in incidence between the groups was 4.9 percentage points or less (Table 49). There were no statistically significant differences between the groups, except for mild redness, which was reported at slightly higher frequency after PCV13 +TIV than after PCV13 (p=0.035). For each of the 4 reactions types, most reports were of mild intensity, and ≤2.6% of reports in either vaccine group were severe.

Table 49 Local Reactions within 14 Days

Table 2-11: Subjects Reporting Local Reactions Within 14 Days After Vaccination – Comparison of 13vPnC+TIV and 13vPnC Alone (Subjects Naive to 23vPS; Studies 3001 and 3008)

	Study 3001 (50-59 Years of Age)					Study 3008 (≥65 Years of Age)				
	13vPnC+TIV/ Placebo Dose 1	Placebo+TIV/ 13vPnC Dose 2				13vPnC+TIV/ Placebo Dose 1	Placebo+TIV/ 13vPnC Dose 2			
Local Reaction	**%**	**%**	**Difference[a]**	**(95% CI[b])**	**p-Value[b]**	**%**	**%**	**Difference[a]**	**(95% CI[b])**	**p-Value[b]**
Redness[c]										
Any	16.3	12.1	4.2	(-1.7, 10.3)	0.163	16.6	12.3	4.3	(-0.4, 9.0)	0.070
Mild	15.7	10.2	5.5	(-0.3, 11.3)	0.061	14.4	9.7	4.7	(0.3, 9.1)	0.035
Moderate	4.2	5.6	-1.5	(-5.5, 2.4)	0.483	6.0	6.1	-0.1	(-3.4, 3.1)	0.978
Severe	0.4	1.2	-0.9	(-3.2, 1.0)	0.332	0.7	1.0	-0.3	(-1.8, 1.2)	0.776
Swelling[c]										
Any	18.4	14.7	3.7	(-2.6, 10.0)	0.249	13.8	10.2	3.6	(-0.7, 8.0)	0.102
Mild	17.0	12.3	4.7	(-1.3, 10.7)	0.123	11.8	8.1	3.7	(-0.3, 7.7)	0.072
Moderate	5.7	6.4	-0.7	(-5.1, 3.6)	0.811	4.2	5.0	-0.8	(-3.7, 2.1)	0.603
Severe	0.4	0.4	-0.0	(-1.9, 1.7)	>.99	0.2	0.0	0.2	(-0.7, 1.3)	0.511
Pain[d]										
Any	86.8	84.5	2.2	(-2.3, 6.8)	0.343	40.0	43.4	-3.4	(-9.7, 3.0)	0.297
Mild	82.8	82.1	0.7	(-4.4, 5.7)	0.807	34.3	37.9	-3.6	(-9.8, 2.6)	0.260
Moderate	39.2	41.1	-1.9	(-9.5, 5.8)	0.650	14.8	19.7	-4.9	(-9.9, 0.1)	0.053
Severe	4.1	4.8	-0.7	(-4.6, 3.0)	0.782	1.4	2.6	-1.2	(-3.4, 0.8)	0.241
Limitation of arm movement[e]										
Any	35.6	42.5	-6.8	(-14.4, 0.8)	0.081	13.9	14.8	-0.9	(-5.6, 3.8)	0.750
Mild	32.6	41.1	-8.6	(-16.1, -1.0)	0.027	13.1	13.4	-0.4	(-4.9, 4.2)	0.898
Moderate	5.2	5.2	-0.0	(-4.1, 4.0)	>.99	1.4	1.0	0.4	(-1.2, 2.2)	0.589
Severe	3.4	2.9	0.5	(-2.8, 3.8)	0.818	1.9	1.4	0.4	(-1.4, 2.4)	0.696

Table 49 Local Reactions within 14 Days (con't)

Table 2-11: Subjects Reporting Local Reactions Within 14 Days After Vaccination – Comparison of 13vPnC+TIV and 13vPnC Alone (Subjects Naive to 23vPS; Studies 3001 and 3008)

	Study 3001 (50-59 Years of Age)					Study 3008 (≥65 Years of Age)				
	13vPnC+TIV/ Placebo Dose 1	Placebo+TIV/ 13vPnC Dose 2				13vPnC+TIV/ Placebo Dose 1	Placebo+TIV/ 13vPnC Dose 2			
Local Reaction	%	%	Difference[a]	(95% CI[b])	p-Value[b]	%	%	Difference[a]	(95% CI[b])	p-Value[b]

a. Difference in proportions, expressed as a percentage.
b. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, 13vPnC+TIV – 13vPnC, expressed as a percentage.
c. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
d. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
e. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Program ID: Study 6115A1-Adult_ISS_EU/CP SAF_LR_SUM_3001_3008_D12.SAS. Runtime ID: 10AUG2010 19:35
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/ISS/Reports, Tables, and Figures/Safety_Locals.zip/saf_lr_sum_d1_d2_3001_3008.htm

Summary regarding Local Reactions:

After an Initial Vaccination of PCV13:

- Pain at the injection site was reported more frequently among subjects <65 years of age (69.2% to 88.8%) than among subjects ≥65 years of age (41.7% to 51.7%).
- The incidence of limitation of arm movement decreased with increasing age: 39.1% to 40.7% among subjects 50 to 59 years of age; 23.5% to 28.5% among subjects 60 to 64 years of age; and 10.5% to 16.2% among subjects ≥65 years of age.
- The incidence of reports varied across studies for redness (10.8% to 20.2%) and swelling (10.0% to 21.7%), with no consistent trends related to subject age.
- In subjects ≥65 years of age, the incidence of each type of local reaction among subjects previously vaccinated with 23vPS (3 to 5 years before study entry) was generally similar to that among subjects naive to 23vPS.

After an Initial Vaccination of PCV13 or 23vPS:

- In subjects 60 to 64 years of age and naive to 23vPS, in both studies, there were no statistically significant differences between groups in the incidence of any of the 4 types of local reactions, **except for pain, which was reported more frequently after vaccination with PCV13 (69.2%)** than after 23vPS (58.3%) (p=0.014) in study 3010.
- In pre-immunized subjects ≥70 years of age, the incidences of redness, swelling, and limitation of arm movement were statistically significantly higher after an initial study vaccination of 23vPS than after an initial study vaccination of PCV13 (p<0.001), while the incidence of pain was slightly higher in the 23vPS group (58.5%) than in the PCV13 group (51.7%) (p=0.062).

After a Subsequent Study Vaccination of PCV13 or 23vPS in subjects 60 to 64 years of age naive to 23vPS:

Comparison of results between initial and subsequent study vaccinations shows that, for all 4 types of local reactions:

- In subjects who received 2 vaccinations of PCV13 1 year apart (PCV13/ PCV13),and in subjects who received 23vPS followed by PCV13 1 year later (23vPS/ PCV13), the incidence and severity of local reactions reported after the subsequent vaccination of PCV13 were no greater than those reported after an initial study vaccination of PCV13; and
- In subjects who received PCV13 followed by 23vPS 1 year later (PCV13/23vPS), the incidence and severity of local reactions reported after the subsequent vaccination of 23vPS were **statistically significantly** greater than those reported after an initial study vaccination of 23vPS. It will be important to evaluate whether the immune response associated with this increased reactogenicity is also statistically significantly increased.

Comparison of results between subsequent study vaccinations shows that, for each of the 4 types of local reactions:

- The incidence of reports after vaccination 2 was statistically significantly higher among subjects receiving PCV13/23vPS than among those receiving PCV13/ PCV13 or 23vPS/ PCV13; and
- The incidence of reports after vaccination 2 was higher in the PCV13/PCV13 group than in the 23vPS/ PCV13group, although the differences between the groups were significant only for redness and for swelling.

After a Subsequent Study Vaccination of PCV13 or 23vPS In subjects ≥70 **years of age naive to 23vPS who had received 1 dose of 23vPS at least 5 years before enrollment:**

Comparison of results between initial and subsequent study vaccinations shows that:

- In subjects who received 2 vaccinations of PCV13 1 year apart (PCV13 /PCV13), the incidence and severity of all 4 types of local reactions reported after the subsequent vaccination of PCV13 were similar to those reported after the initial study vaccination of PCV13; and
- In subjects who received 23vPS followed by PCV13 1 year later (23vPS/ PCV13), the incidence and severity of redness, swelling, and pain reported after the subsequent vaccination of PCV13 were similar to those reported after an initial study vaccination of , PCV13 while the incidence of limitation of arm movement was statistically significantly higher after vaccination 2 of 23vPS/ PCV13 (19.9%) than after the initial dose of PCV13 (10.5%).

Comparison of results between subsequent study vaccinations shows that:

- For all 4 types of local reactions, the incidence and severity reported after vaccination 2 were similar in the 23vPS/PCV13v group and the PCV13/ PCV13 group.

Concomitant Administration of PCV13 and TIV:

- In naive subjects 50 to 59 years of age, and in naive subjects ≥65 years of age, the incidence and severity of each of the 4 types of local reactions after administration of PCV13 +TIV were similar to those after PCV13 alone.

8.1.7 Solicited Systemic Events

The incidence of systemic events reported within 14 days after an initial study vaccination of PCV13 is summarized for all 6 studies.

After an initial vaccination of PCV13, the incidence of **fever (temperature ≥38°C)** was similar across all 6 studies, with no apparent differences among the various age groups. As shown in the table, the percentage of subjects reporting **any fever** (≥38°C) ranged from 1.0% (study 3005) to 7.7% (study 004). However, all reports of fever >40°C (>104.0°F) after vaccination 1 were confirmed to be e-diary data entry errors. When these values were excluded from the analyses, the incidence of fever ranged from 1.0% (study 3005) to 4.2% (study 3010). In all of these studies, **most reports of fever were mild (<38.5°C)**, and the incidence of **severe fever (≥39°C but ≤40°C**) was ≤0.4%.

All other types of systemic events were consistently reported at lower incidence among subjects ≥65 years of age (studies 3008, 3000, and 3005) than among younger subjects (studies 004, 3001, and 3010). This held true for each type of systemic event as well as for the use of medications to treat pain and fever. In each age group (50 to 59, 60 to 64, and ≥65 years of age), the **systemic events reported most frequently were fatigue, headache, and new generalized muscle pain**. Overall, rash and vomiting were reported least often (<10% in most studies). Because of the differences in the incidence of systemic events among the studies associated with subject age, **comparison of data between naive and pre-immunized subjects is best done using data for groups of subjects of similar age.**

Naive Subjects

<u>In study 004</u>, all types of systemic events were reported at similar incidence in the PCV13 and 23vPS groups, with no statistically significant differences in incidence between the groups (Table 52). All reports of fever >40°C (>104.0°F) were confirmed to be e-diary data entry errors. When these values were excluded from the analyses, the incidence of fever was 4.0% after PCV13 and 1.1% after 23vPS . In the PCV13 group, mild fever (≥38°C but <38.5°C) was reported for 7 subjects (3.9%) and moderate fever (≥38.5°C but <39°C) was reported for 1 subject (0.6%); in the 23vPS group, mild fever was reported for 2 subjects (1.1%). The most frequently reported types of systemic events in both the PCV13 and the 23vPS groups, respectively, were fatigue (63.2%, 61.5%), new generalized muscle pain (56.2%, 57.8%), and headache (54.0%, 54.4%).

<u>In study 3010</u>, temperatures of >40°C were recorded on 12 days for 1 subject (0.4%) in the PCV13 group; however, the site confirmed with the subject that these were all e-diary data entry errors. After excluding these erroneous values, the incidence of fever (≥38°C) was 4.2% after PCV13, compared with 1.6% after 23vPS (However, the use of medication to treat fever was reported more frequently among subjects vaccinated with

23vPS (17.5%) than among subjects vaccinated with PCV13 (8.6%) (p=0.012). In the PCV13 group, most occurrences of fever were mild (<38.5°C), and in the 23vPS group, mild fever was reported for 1 subject (0.8%) and severe fever (≥39°C but ≤40°C) was reported for 1 subject (0.8%). Fatigue, headache, and new generalized muscle pain were the most frequently reported types of events in both vaccine groups. Most types of events were reported at similar incidence in both vaccine groups, with the exceptions being events that were reported at significantly lower incidence in the PCV13 vaccine group than in the 23vPS group, respectively: decreased appetite (14.7%, 23.0%; p=0.038), aggravated generalized muscle pain (22.0%, 32.5%; p =0.020), and new generalized joint pain (15.5%, 23.8%; p=0.040). Fever was the only systemic event that was graded. See systemic reactogenicity data for cohorts 1 (age 60-64 yrs) and cohort 2 (age 50-59 yrs) from study 004 depicted in Tables 50 and 51 below.

Table 50 Systemic Events within 14 days of Vaccination (Age 60-64 years)

Table 10-4: Subjects Reporting Systemic Events Within 14 Days After Vaccination, Age 60-64 Years (Cohort 1) - Safety Population

	Vaccine Group (as Administered) 60-64 Years Old (Cohort 1)										
	13vPnC				23vPS						
Systemic Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])	p-Value[e]
Fever											
Any (≥38°C)	181	14	7.7	(4.3, 12.6)	185	11	5.9	(3.0, 10.4)	1.8	(-3.6, 7.3)	0.522
Mild (≥38°C but <38.5°C)	179	7	3.9	(1.6, 7.9)	180	2	1.1	(0.1, 4.0)	2.8	(-0.6, 6.9)	0.098
Moderate (≥38.5°C but <39°C)	178	1	0.6	(0.0, 3.1)	179	0	0.0	(0.0, 2.0)	0.6	(-1.5, 3.1)	0.527
Severe (≥39°C but ≤40°C)	177	0	0.0	(0.0, 2.1)	179	0	0.0	(0.0, 2.0)	0.0	(-2.1, 2.1)	>0.99
Potentially life threatening (>40°C)	180	8[f]	4.4	(1.9, 8.6)	184	9[f]	4.9	(2.3, 9.1)	-0.4	(-5.2, 4.2)	0.905
Fatigue	277	175	63.2	(57.2, 68.9)	273	168	61.5	(55.5, 67.3)	1.6	(-6.5, 9.8)	0.717
Headache	252	136	54.0	(47.6, 60.2)	259	141	54.4	(48.2, 60.6)	-0.5	(-9.1, 8.3)	0.930
Chills	204	48	23.5	(17.9, 30.0)	199	48	24.1	(18.4, 30.7)	-0.6	(-9.0, 7.8)	0.919
Rash	194	32	16.5	(11.6, 22.5)	192	25	13.0	(8.6, 18.6)	3.5	(-3.7, 10.7)	0.344
Vomiting	180	7	3.9	(1.6, 7.8)	186	10	5.4	(2.6, 9.7)	-1.5	(-6.2, 3.1)	0.546
Decreased appetite	202	43	21.3	(15.9, 27.6)	207	45	21.7	(16.3, 28.0)	-0.5	(-8.5, 7.6)	0.937
New generalized muscle pain	249	140	56.2	(49.8, 62.5)	268	155	57.8	(51.7, 63.8)	-1.6	(-10.2, 7.0)	0.715
Aggravated generalized muscle pain	215	70	32.6	(26.3, 39.3)	225	84	37.3	(31.0, 44.0)	-4.8	(-13.8, 4.2)	0.297
New generalized joint pain	197	48	24.4	(18.5, 31.0)	216	65	30.1	(24.1, 36.7)	-5.7	(-14.4, 2.9)	0.195
Aggravated generalized joint pain	205	51	24.9	(19.1, 31.4)	206	44	21.4	(16.0, 27.6)	3.5	(-4.7, 11.8)	0.416
Any systemic event[g]	327	270	82.6	(78.0, 86.5)	330	271	82.1	(77.6, 86.1)	0.4	(-5.4, 6.3)	0.907

a. N = Number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects.
d. Difference in proportions, expressed as a percentage.
e. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, 13vPnC – 23vPS, expressed as a percentage.
f. All reports of fever >40°C were confirmed as data entry errors.
g. Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

Program ID: Study 6115A1-004/CP SAF_SE_WITHIN.SAS. Runtime ID: 24JUN2010 12:46
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Table 51 Systemic Events within 14 days after Vaccination (50-59 Years of Age)

Table 10-5: Subjects Reporting Systemic Events Within 14 Days After Vaccination, Age 50-59 Years (Cohort 2) - Safety Population

	Vaccine Group (as Administered) 13vPnC 50-59 Years Old (Cohort 2)			
Systemic Event	**N[a]**	**n[b]**	**%**	**(95% CI[c])**
Fever				
Any (≥38°C)	137	2	1.5	(0.2, 5.2)
Mild (≥38°C but <38.5°C)	137	2	1.5	(0.2, 5.2)
Moderate (≥38.5°C but <39°C)	136	0	0.0	(0.0, 2.7)
Severe (≥39°C but ≤40°C)	136	0	0.0	(0.0, 2.7)
Potentially life threatening (>40°C)	136	0	0.0	(0.0, 2.7)
Fatigue	248	157	63.3	(57.0, 69.3)
Headache	246	162	65.9	(59.6, 71.8)
Chills	158	31	19.6	(13.7, 26.7)
Rash	148	21	14.2	(9.0, 20.9)
Vomiting	144	10	6.9	(3.4, 12.4)
Decreased appetite	166	42	25.3	(18.9, 32.6)
New generalized muscle pain	238	147	61.8	(55.3, 68.0)
Aggravated generalized muscle pain	188	75	39.9	(32.8, 47.3)
New generalized joint pain	165	52	31.5	(24.5, 39.2)
Aggravated generalized joint pain	168	43	25.6	(19.2, 32.9)
Any systemic event[d]	314	265	84.4	(79.9, 88.2)

a. N = Number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects.
d. Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

Program ID: Study 6115A1-004/CP SAF_SE_WITHIN.SAS. Runtime ID: 24JUN2010 12:46
Source: Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/004/Reports, Tables, and Figures/Safety_Systemic/Safety_Systemic_Final.ZIP/saf_se_postv1_14_c2.htm

Table 52 Systemic Events within 14 Days After an Initial Study Vaccination (60-64 Years of Age)

Table 2-13: Subjects Reporting Systemic Events Within 14 Days After an Initial Study Vaccination – Comparison of 13vPnC and 23vPS (Subjects Naive to 23vPS, 60-64 Years of Age)

	Study 004					Study 3010				
Systemic Event	13vPnC %	23vPS %	Difference[a]	(95% CI[b])	p-Value[b]	13vPnC %	23vPS %	Difference[a]	(95% CI[b])	p-Valu
Fever										
Any (≥38°C)	7.7	5.9	1.8	(-3.6, 7.3)	0.522	4.6	1.6	3.0	(-1.2, 6.6)	0.137
Mild (≥38°C but <38.5°C)	3.9	1.1	2.8	(-0.6, 6.9)	0.098	3.8	0.8	3.0	(-0.6, 6.3)	0.088
Moderate (≥38.5°C but <39°C)	0.6	0.0	0.6	(-1.5, 3.1)	0.527	0.8	0.0	0.8	(-2.0, 2.8)	0.457
Severe (≥39°C but ≤40°C)	0.0	0.0	0	(-2.1, 2.1)	>.99	0.4	0.8	-0.4	(-3.8, 1.6)	0.690
Potentially life threatening (>40°C)[c]	4.4[c]	4.9[c]	-0.4	(-5.2, 4.2)	0.905	0.4[c]	0.0	0.4	(-2.4, 2.3)	0.780
Fatigue	63.2	61.5	1.6	(-6.5, 9.8)	0.717	50.5	49.1	1.3	(-7.9, 10.6)	0.781
Headache	54.0	54.4	-0.5	(-9.1, 8.3)	0.930	49.7	46.1	3.6	(-5.8, 12.9)	0.460
Chills	23.5	24.1	-0.6	(-9.0, 7.8)	0.919	19.9	26.9	-7.0	(-15.9, 1.4)	0.108
Rash	16.5	13.0	3.5	(-3.7, 10.7)	0.344	8.6	13.4	-4.8	(-12.2, 1.7)	0.153
Vomiting	3.9	5.4	-1.5	(-6.2, 3.1)	0.546	3.1	3.1	0.0	(-4.6, 3.6)	>.99
Decreased appetite	21.3	21.7	-0.5	(-8.5, 7.6)	0.937	14.7	23.0	-8.2	(-16.7, -0.4)	0.038
New generalized muscle pain	56.2	57.8	-1.6	(-10.2, 7.0)	0.715	46.9	51.5	-4.6	(-13.9, 4.8)	0.349
Aggravated generalized muscle pain	32.6	37.3	-4.8	(-13.8, 4.2)	0.297	22.0	32.5	-10.4	(-19.6, -1.6)	0.020
New generalized joint pain	24.4	30.1	-5.7	(-14.4, 2.9)	0.195	15.5	23.8	-8.3	(-16.9, -0.4)	0.040
Aggravated generalized joint pain	24.9	21.4	3.5	(-4.7, 11.8)	0.416	14.0	21.1	-7.2	(-15.5, 0.5)	0.068
Use of medication to treat pain	N/A	N/A				31.3	32.7	-1.3	(-10.6, 7.6)	0.779
Use of medication to treat fever	N/A	N/A				8.6	17.5	-8.9	(-16.6, -1.9)	0.012

Abbreviation: N/A = not applicable.

a. Difference in proportions, expressed as a percentage.

b. Exact 2-sided confidence interval and corresponding p-value (based on Chan & Zhang) for the difference in proportions, 13vPnC – 23vPS, expresse as a percentage.

c. In both studies 004 and 3010, all reports of fever >40°C were confirmed to be the result of e-diary data entry errors.

Program ID: Study 6115A1-Adult_ISS_EU/CP SAF_SE_SUM_004_3010.SAS. Runtime ID: 04AUG2010 02:30

Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6115 13VPNC ADULT/ISS/Reports, Tables, and Figures/Safety_Systemic.zip/saf_se_sum_004_3010.htm (modified)

Comparisons Between Subsequent Vaccinations of PCV13 or 23vPS

The results of analyses comparing the incidence of systemic events after subsequent vaccinations of PCV13 or 23vPS (after vaccination 2 of the PCV13/PCV13, PCV13/23vPS, and 23vPS/PCV13 regimens). After excluding erroneous values from the analysis, fever was reported at similar incidence after PCV13/PCV13 (1.3%), PCV13/23vPS (3.1%), and 23vPS/PCV13 (0.9%) (p=0.514). For most types of systemic events, the incidence was highest after PCV13/23vPS; however, differences among the 3 groups were statistically significant for only 3 types of events: rash, new generalized muscle pain, and aggravated generalized muscle pain. The use of medication to treat pain was also reported most frequency after PCV13/23vPS (p<0.001). Fever, vomiting, decreased appetite, and aggravated generalized joint pain were reported at similar incidence among the 3 groups. Pair-wise comparisons showed no statistically significant differences between the PCV13/PCV13 and 23vPS/PCV13 groups in the incidence of any systemic events.

Comparisons Between Initial and Subsequent Vaccinations of PCV13 in Pre-immunized Subjects

In study 3005, systemic events reported after PCV13/PCV13 (vaccination 2) were compared with those reported after PCV13 (vaccination 1) using data for subjects in the PCV13/PCV13 group who received both vaccinations. The incidence of systemic events reported after administration of PCV13/PCV13 was similar to the incidence of events after the initial dose of PCV13 for all types of systemic events except chills, which were reported more often after PCV13 (9.3%) than after PCV13/PCV13 (4.4%) (95% CI on the difference = -9.6, -0.2). The most frequently reported types of systemic events were

fatigue, headache, new generalized muscle pain, and aggravated generalized muscle pain, both after PCV13and after PCV13/ PCV13. Mild fever was reported for 3 subjects (1.7%) after the initial vaccination of PCV13 and for 1 subject (0.6%) after PCV13/ PCV13; severe fever was reported for 1 subject (0.6%) after PCV13/PCV13. In addition, potentially life-threatening fever was reported for 2 subjects (1.1%) after PCV13/ PCV13. The value for one of these subjects was confirmed to be an e-diary data entry error. The other subject had a confirmed temperature of 104.4°F on day 2 after PCV13/ PCV13. After excluding the erroneous value, the incidence of any fever ≥38°C was 1.1% after PCV13/ PCV13 compared with 1.7% after PCV13. The incidence of systemic events reported after 23vPS/ PCV13 (vaccination 2) was similar to the incidence reported after the initial vaccination of PCV13 for all types of systemic events as well as for the use of medications to treat pain and fever , with no statistically significant differences between the groups. The report of fever >40°C for 1 subject after 23vPS/ PCV13 was confirmed to be an e-diary data entry error. After excluding this value from the analysis, the incidence of fever after 23vPS/ PCV13 was 1.8% compared with 1.0% after PCV13.

Summary Regarding Solicited Systemic Events
Systemic events that were monitored by subjects for 14 days after each vaccination and recorded in e-diaries included fever, chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain.

After an initial vaccination of PCV13, most systemic events were mild, and severe systemic events were infrequent. Fever (temperatures (≥38°C) was reported at similar incidence and severity across studies, regardless of subject age. All other types of systemic events were, in general, reported more frequently among subjects <65 years of age than among older subjects. The incidence and intensity of systemic events did not differ between naive and pre-immunized subject**s.**

In naive subjects 60 to 64 years of age and preimmunized subjects ≥ 70 years of age: Most types of systemic events were reported at similar incidence after administration of PCV13 or 23vPS, although a few types of events (including muscle pain and joint pain) were reported more frequently after 23vPS than after PCV13. The most frequently reported types of systemic events reported after PCV13 and after 23vPS were fatigue, headache, and muscle pain. When PCV13 was administered as a subsequent study vaccination one year after an initial study vaccination of either PCV13 (PCV13/ PCV13) or 23vPS (23vPS/ PCV13), the incidence of each type of systemic event was similar to or lower than that observed after an initial study vaccination of PCV13. Similarly, when 23vPS was administered as a subsequent study vaccination one year after an initial study vaccination of PCV13 (PCV13/23vPS), the incidence of each type of systemic event was similar to or lower than that observed after an initial study vaccination of 23vPS.

When PCV13 was administered to naive subjects concomitantly with trivalent inactivated influenza vaccine (TIV): Both in younger subjects (50 to 59 years of age) and in older subjects (≥65 years of age), fever ≥ 38°C was reported infrequently and at similar incidence after concomitant. Among younger subjects (50 to 59 years of age), for

most types of systemic events, the incidence of reports after PCV13 +TIV was similar to that after PCV13 alone, but was statistically significantly higher than that after administration of TIV alone. Among older subjects (≥65 years of age), 6 types of systemic events were reported at statistically higher incidence after administration of PCV13+TIV than after PCV13 alone (fatigue, headache, chills, decreased appetite, new joint pain, and aggravated joint pain), while most systemic events were reported at similar incidence after PCV13+TIV and after TIV alone.

8.1.8 Unsolicited Systemic Events

- In all studies, the AEs reported were generally the types of diseases and conditions often observed in adults over 50 years of age.
- The incidence and types of AEs reported within 1 month after administration of PCV13 were similar across studies and did not differ between naive and pre-immunized subjects.
- The incidence and types of AEs reported after administration of PCV13, in general, did not appear to be influenced by subject age, except that at the 6-month follow-up, the incidence of serious AEs was slightly lower among subjects 50 to 59 years of age (1.2% to 1.8%) than among subjects 60 to 64 years of age (2.9% to 3.1%), and was highest among subjects ≥65 years of age (3.9% to 5.8%).
- The incidence and types of AEs reported after administration of PCV13 were, in general, similar to those observed after the administration of 23vPS.
- The incidence and types of AEs reported after a subsequent vaccination administered as PCV13/ PCV13 or PCV13/23vPS were similar, in general, to those reported after an initial study dose of PCV13.
- In naive subjects 60 to 64 years of age the incidence and types of AEs reported after PCV13/23vPS were generally similar to those observed after an initial study vaccination of 23vPS.
- When the incidence and types of AEs reported for naive subjects receiving concomitant PCV13+TIV were compared with those reported for naive subjects receiving PCV13 alone or TIV alone, there were some statistically significant differences between the vaccine groups in the incidence of adverse events (both for all AEs and for individual types of AEs), the actual differences between groups in the percentage of subjects reporting AEs were small.
- A total of 16 subjects died during the 6 primary studies of PCV13: 12 (0.21%) of the 5667 subjects who received PCV13; and 4 (0.29%) of the 1391 subjects who received 23vPS.
- None of the deaths appeared to be related to study vaccine.
- Only 2 SAEs occurring after administration of 13vPnC were considered by the investigator to be at least possibly related to study vaccine idiopathic thrombocytopenic purpura and Guillain-Barré syndrome, both of which resolved.

Safety in Males versus Females

The Applicant evaluated safety and tolerability of PCV13 separately for males and females, using data for naive subjects 60 to 64 years of age (study 004) and for pre-immunized subjects ≥70 years of age (study 3005). The results show that after an initial vaccination of PCV13, all 4 types of local reactions were generally reported at higher

incidence in females than in males. In naive subjects 60 to 64 years of age, most systemic events were reported at higher incidence among females than in males, while in pre-immunized subjects ≥70 years of age, most systemic events were reported at similar incidence in males and females. In both studies, the incidence and types of AEs, related AEs, and serious AEs were generally similar for males and females, although a notable exception was that, in pre-immunized subjects ≥70 years of age, the incidence of serious AEs reported at the 6-month follow-up contact after both vaccination 1 and after vaccination 2 was somewhat higher in males than in females.

Summary of Safety in Adults 50 years of age and older

The Applicant evaluated the safety of PCV13 based on data from 6 adult studies in which a total of 5,667 subjects 50 to 93.5 years of age received at least one dose of PCV13. A total of 3,051 of the subjects were 65 years of age or older. Four of the six studies involved naïve subjects (subjects who had no prior receipt of Pneumovax23) and two studies involved adults who had previously received Pneumovax23.

Overall, based on the results of the 6 clinical studies, the reactogenicity profile of PCV13has been shown to be acceptable in pneumococcal polysaccharide vaccine naïve and in pre-immunized adults. No major concerns were raised regarding serious adverse events. Limitations included the size of the safety database which may be too small to detect rare AEs occurring at a frequency lower than 0.1%. The Applicant will submit safety and efficacy data from the 84,500 subjects in the confirmatory efficacy study (6115A1-3006; Community-Acquired Pneumonia Immunization Trial in Adults [CAPITA]) conducted in the Netherlands.

Several points regarding local and systemic adverse events that occur in adults receiving Prevnar13:

Statistically significantly increased adverse events for PCV13 as an initial or subsequent vaccine in a dosing schedule include the following:

After an initial vaccination of PCV13 or 23vPS:

- In subjects 60 to 64 years of age and naive to 23vPS, pain was reported more frequently after vaccination with PCV13 (69.2%) than after 23vPS (58.3%) (p=0.014) in study 3010.

After a subsequent vaccination of PCV13 or 23vPS

- In subjects who received PCV13 followed by 23vPS one year later (PCV13/23vPS), the incidence and severity of local reactions reported after the subsequent vaccination of 23vPS were statistically significantly greater than those reported after an initial study vaccination of 23vPS.

After a subsequent vaccination of PCV13 or 23vPS in subjects 60 to 64 years of age naive to 23vPS:

- The incidence of reports after vaccination 2 was statistically significantly higher among subjects receiving PCV13/23vPS than among those receiving PCV13/PCV13 or 23vPS/PCV13; and
- The incidence of reports after vaccination 2 was higher in the PCV13/PCV13 group than in the 23vPS/ PCV13 group, although the differences between the groups were significant only for redness and for swelling

- In subjects who received 23vPS followed by PCV13 at 1 year later (23vPS/PCV13), the incidence and severity of redness, swelling, and pain reported after the subsequent vaccination of PCV13 were similar to those reported after an initial study vaccination of PCV13, while the incidence of limitation of arm movement was statistically significantly higher after vaccination 2 of 23vPS/PCV13 (19.9%) than after the initial dose of PCV13 (10.5%).
- Among younger subjects (50 to 59 years of age), for most types of systemic events, the incidence of reports after PCV13+TIV was similar to that after PCV13 alone, but was statistically significantly higher than that after administration of TIV alone.
- Among older subjects (≥65 years of age), 6 types of systemic events were reported at statistically higher incidence after administration of PCV13+TIV than after PCV13 alone (fatigue, headache, chills, decreased appetite, new joint pain, and aggravated joint pain).

9.0 Post Marketing plans

9.1 Routine pharmacovigilance for Prevnar 13 in children

At the time of licensure, the applicant agreed to comply with the requirements of 21 CFR 600.80. In addition, the applicant agreed to submit a monthly line listing of all non-15 day adverse event reports to the FDA vaccine adverse events reporting system (VAERS) contractor for the first 3 years, as it did for PCV7. The applicant also agreed to include a description of each individual adverse event report, along with frequency distributions of Medical Dictionary of Regulatory Activities (MedDRA) terms for these reports. One listing should identify every MedDRA Preferred Term (PT). Another will group the PTs into higher level categories to facilitate recognition of patterns (System Organ Class (SOC), High Level Group Term (HLGT), and High Level Term (HLT). The applicant also agreed to provide the cumulative number of U.S doses distributed with each of these monthly submissions. As of this date the applicant has diligently complied with this agreement.

9.2. Postmarketing safety surveillance of PCV13 in children

As part of the licensing agreement, the applicant is conducting a post-licensure observational safety study in collaboration with Northern California Kaiser Permanente (NCKP) using a safety cohort of children who received PCV13 as part of routine medical care (study protocol 609A1-4002). The overall objective of the study is to expand the understanding of the safety profile of PCV13 in routine use following licensure. This study was reviewed with the initial application and is ongoing. The study population is estimated at 60,000 children, including 43,000 infants who receive 3 doses of PCV13 primary series at NCKP and any children who receive at least one dose of PCV13 at NCKP during the course of accruing the 43,000 completed primary series vaccinations. Historical controls will be comprised of two distinct groups, a “7v cohort” composed of children who received a complete series of PCV7 before introduction of PCV13 and a”7v/13v cohort” comprised of children who received any combination of PCV7 and PCV13. The study is expected to be completed in 2014 (4 years from the start of PCV13 use in routine practice). The submission of the interim report is expected no later than 27 months after study start, and the final report no later than 6 months after the last of the 43,000 children has received his or her third dose.

The pharmacovigilance plan for the pediatric indication, including the phase 4 safety study, was presented at the November 18, 2009 VRBPAC meeting**.** The Committee agreed that the available data were adequate to support the safety of PCV13 when administered to infants and toddlers at 2, 4, 6, and 12-15 months of age. The Committee discussed the proposed phase 4 study and commented specifically on the safety of PCV13 in children at “higher risk” of IPD and asked that infants and toddlers with solid organ transplants be included in the “high risk” groups. The Committee also discussed the potential risk of autoimmune diseases with additional doses of CRM_{197} protein with recommended routine infant and toddler vaccination series. The Committee asked that arthralgia be included in the list of pre-specified events of interest and that 6 months of follow-up be considered to assess this potential risk for late onset diagnoses. The applicant agreed to these requests.

In the final report of the post marketing Phase 4 safety study, the applicant plans to include sub-analyses for these groups and for children with reactive airway disease. Based on recommendations made at the November 18, 2009, VRBPAC meeting, the applicant had included organ transplant recipients as a high risk group for sub-analyses of data from the phase 4 safety study infants/children.

In addition, the applicant agreed with CBER's request to analyze additional safety concerns if they are identified through VAERS, the applicant's database, or other data sources during the course of the post-licensure safety study. The decision of what constitutes a safety concern warranting further investigation in the post-licensure safety study will be based on the collaborative judgment of CBER and the applicant.

9.3 Study 6115A1-3006-NL – Phase 4 study of Prevnar 13 in adults

The applicant is conducting a large-scale, randomized, placebo-controlled, double-blind trial (Study 6115A1-3006) in which 85,000 subjects (42,500 per group) aged 65 years or older will receive a single dose of PCV13 or placebo. The study is being carried out in multiple centers in the Netherlands. This study will assess the safety profile of PCV13 and measure the incidence of serious adverse events for 6 months after vaccination for those in the immunogenicity subset (N=2,000) and for 28 days after vaccine administration in the remaining subjects (N=83,000). With such a design, detection and assessment of rare events including autoimmune disease is unlikely. The study will also evaluate the incidence rates of local reactions and systemic events specifically identified in clinical trials and other adverse events for all subjects in the immunogenicity subset and within different age and gender groups. Adverse events, including local reactions and systemic reactions, will also be summarized by age (subjects aged < 75 years and ≥ 75 years) and gender. SAEs, including deaths, will be categorized according to the MedDRA dictionary. Deaths will be recorded for the duration of the study and will be evaluated. This study will also assess the efficacy of the PCV13 in the prevention of the first episode of confirmed vaccine-type (VT) pneumococcal CAP and IPD.

10.0 References

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